Resistant HTN: Updates in Management

By

Mohammed Kamal Nassar

Assistant Lecturer of Nephrology

Mansoura University

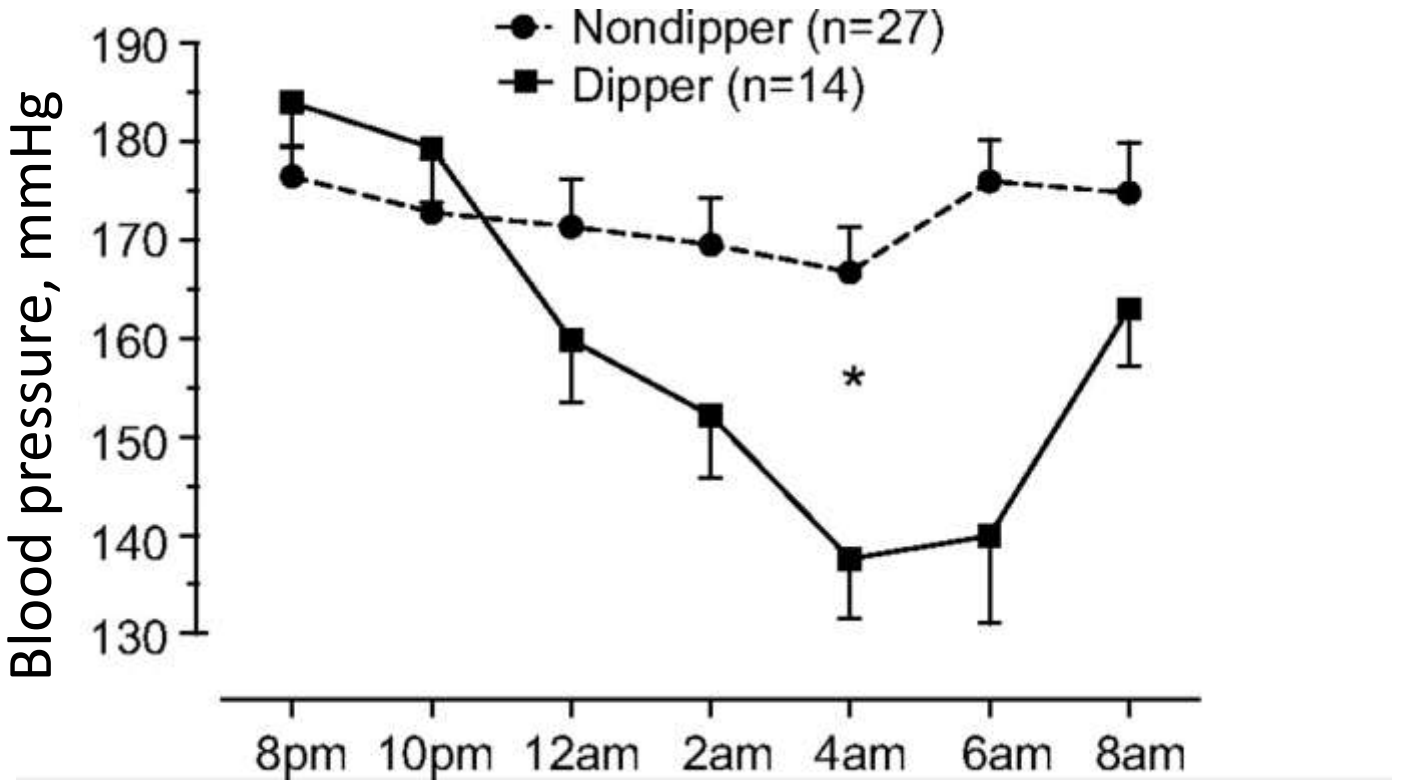
Resistant HTN

- Failure to reach BP goal despite using at least **3** antihypertensive medications in **adequate** dosages (including at least one **diuretic**):
  - Office: ≤ 140/90 mmHg or ≤ 130/80 mmHg (in **DM** & **CKD**)
  - ABPM: Daytime < 135/85 mmHg, nighttime < 120/70 mmHg
- Using ≥ **4** drugs, independent of BP control, can also be diagnosed as RH.

Calhoun et al., Hypertension 2008; 51: 1403–1419

- Lack of nocturnal decrease of blood pressure ("**non-dipper**") in 24-hour ABPM is considered to be resistant.

Rios et al., Chronobiol Int 2013; 30: 207–20



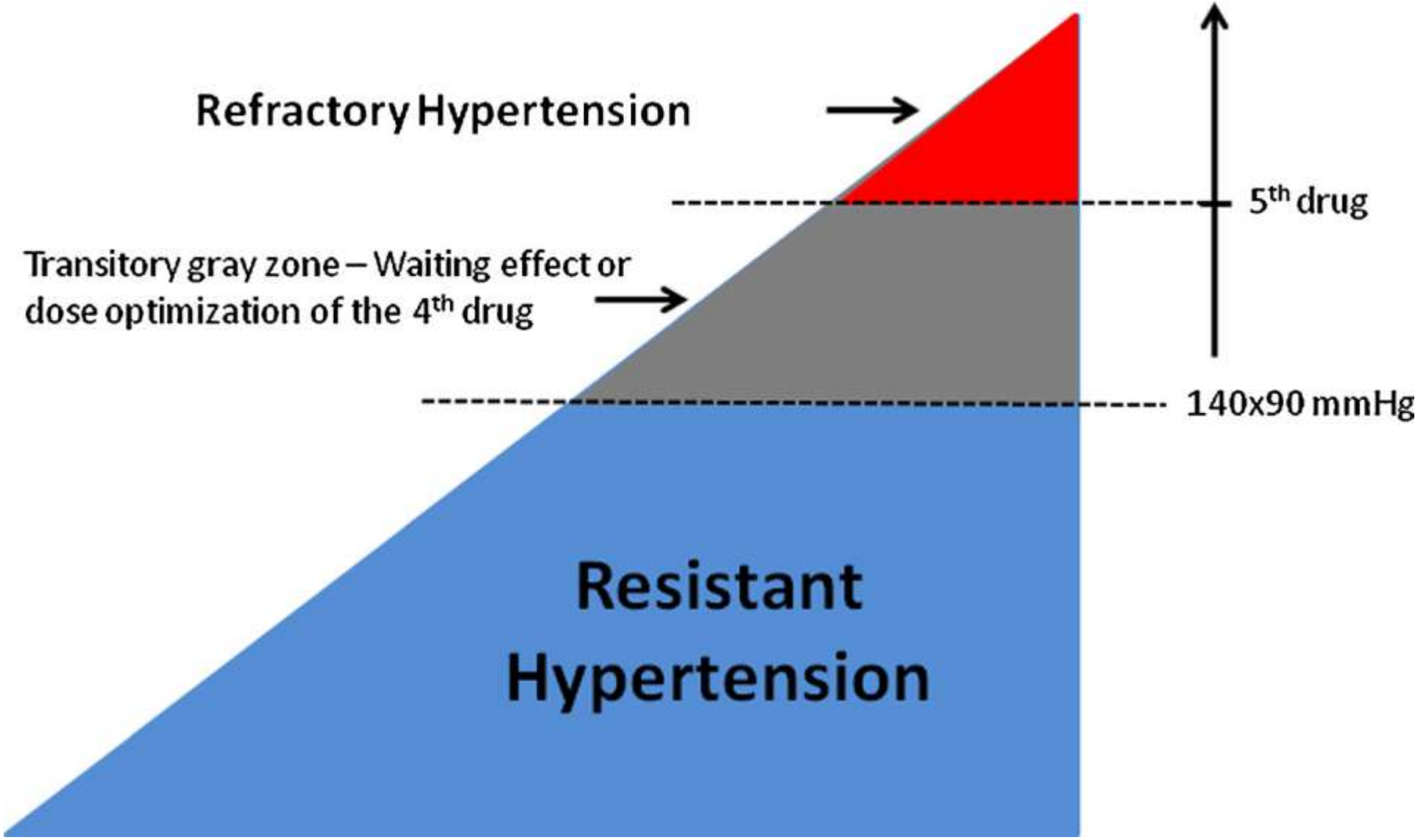
Refractory HTN

- Uncontrolled resistant hypertension after at least three visits to the clinic

Acelajado et al., J Clin Hypertens. 2012;14(1):7–12

- Uncontrolled after ≥ 5 drugs.

Calhoun et al., Hypertension. 2014; 63(3):451–8



Modolo et al., Curr Hypertens Rep 2014;16:485

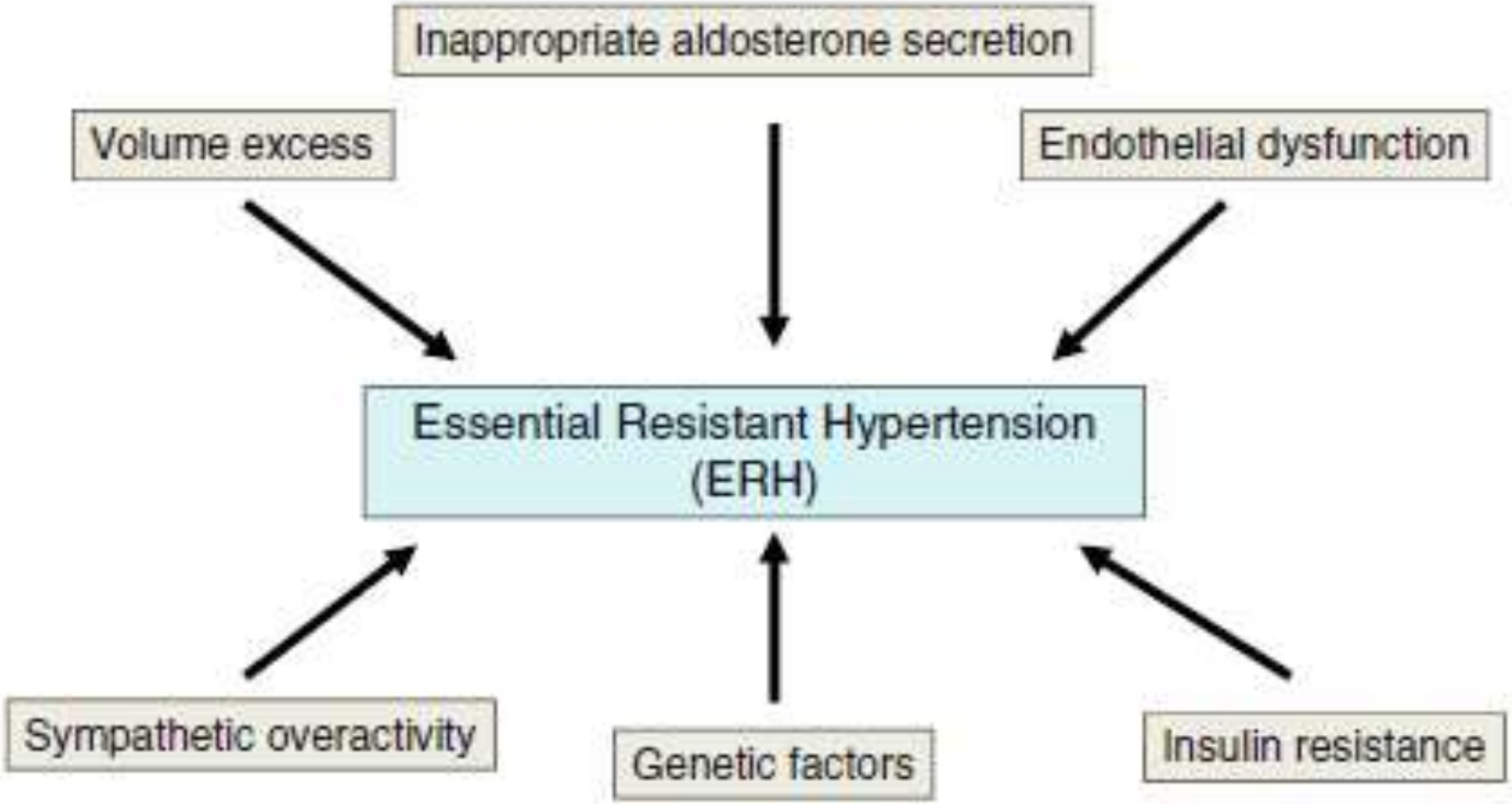
Prevalence

- 10– 30% of all hypertensives.

- Increasing prevalence in the last years

Egan et al., Circulation 2011; 124: 1046–1058.

Pathogenesis



Veglio et al., High Blood Press Cardiovasc Prev;2013(20): 251–256

Is It Important ?

RH in Pubmed Publications

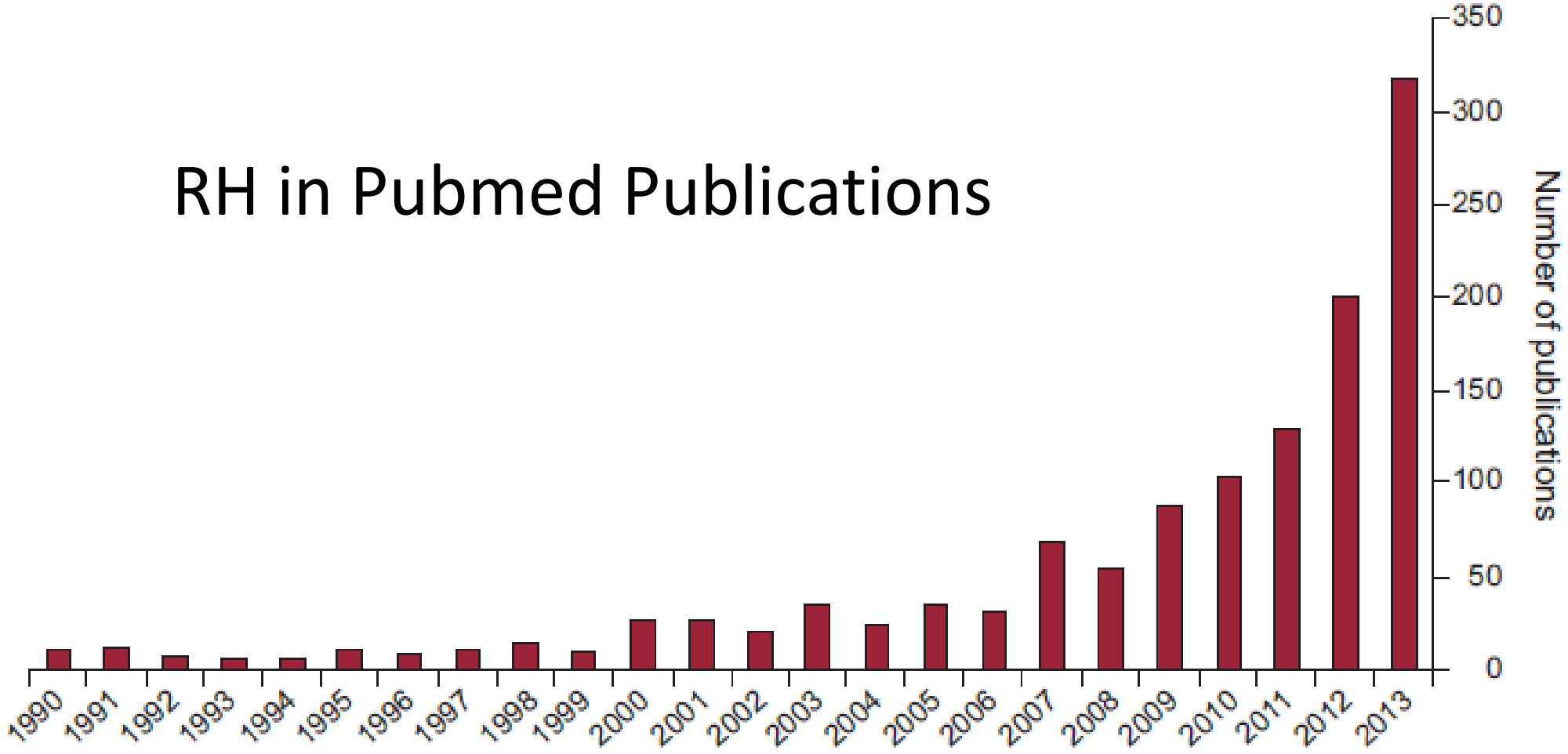


Figure. Publications containing the descriptor "resistant hypertension" in the title or abstract.

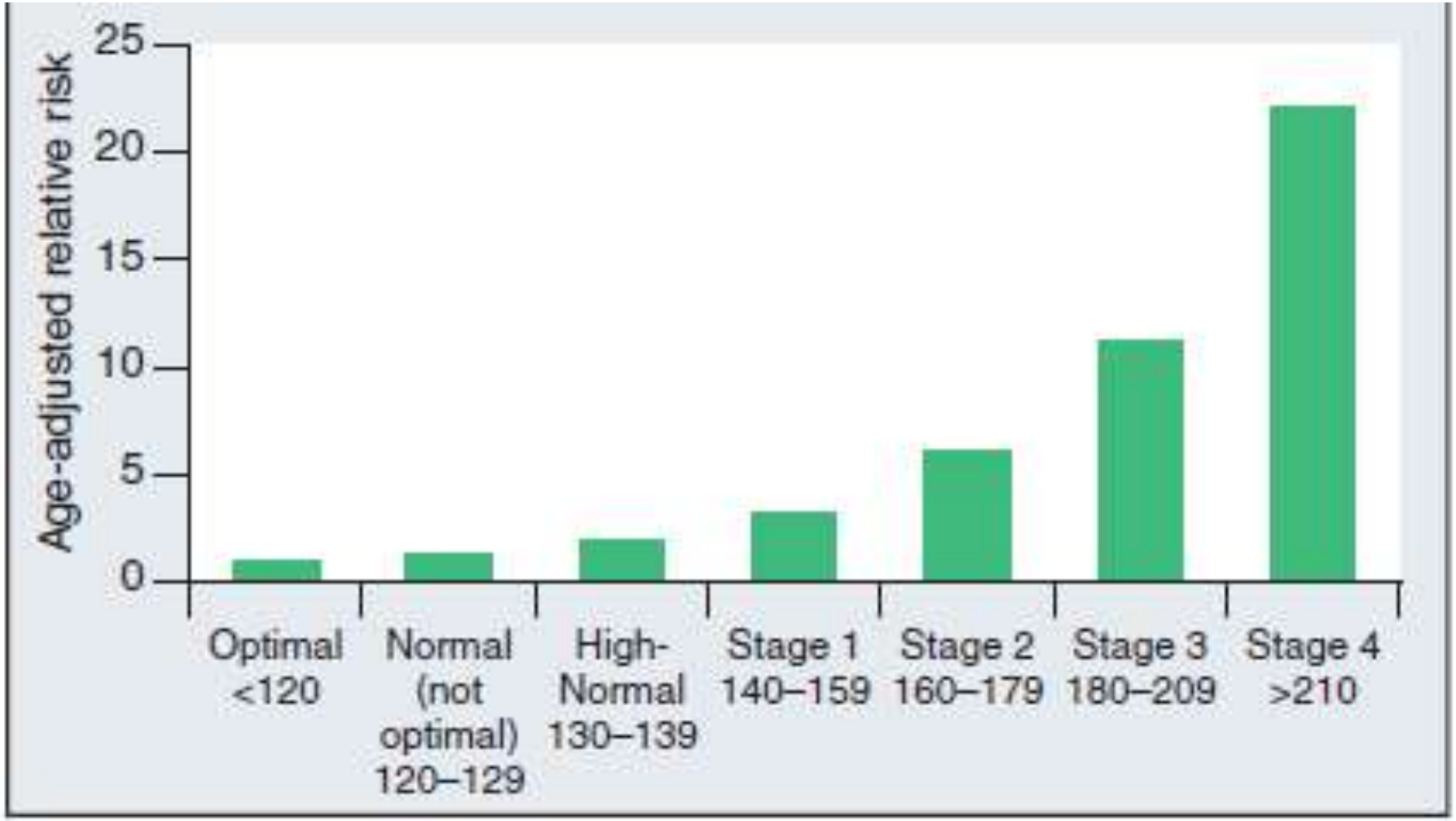
J. Redon / Rev Esp Cardiol. 2014;67(4):251–253

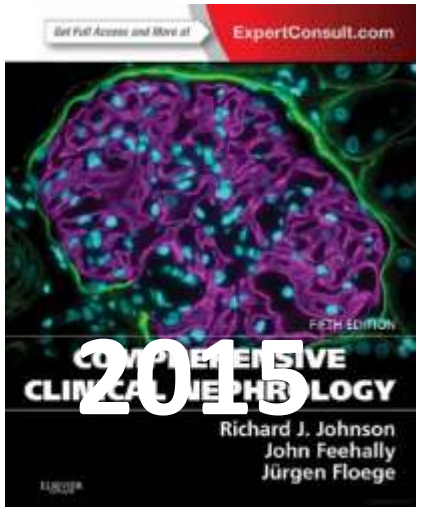
Why Important ?

	cohort (n = 111,986)***			
	RH	Non-RH	Adjusted HR (95% CI)**	*P* value
Outcomes	No. (%)	No. (%)		
MACE	2,283 (13.9)	9,573 (10.0)	1.17 (1.09–1.26)	<0.001
All-cause mortality	882 (5.4)	3,712 (3.9)	1.06 (0.95–1.19)	0.312
Acute coronary syndrome*	459 (2.8)	1,686 (1.8)	1.17 (0.99–1.39)	0.070
Stroke*	1,933 (11.8)	8,278 (8.7)	1.17 (1.08–1.27)	<0.001
Ischemic stroke*	1,209 (7.4)	5,026 (5.3)	1.34 (1.20–1.48)	<0.001
Hemorrhagic stroke*	345 (2.1)	1,622 (1.7)	0.96 (0.80–1.15)	0.634
Unclassified stroke*	379 (2.3)	1,630 (1.7)	0.96 (0.80–1.14)	0.625

Hung et al., 2014.PLoS ONE 9(8): e104362

CKD & ESRD


Age-adjusted relative risk
25
20
15
10
5
0
Optimal <120
Normal (not optimal) 120–129
High-Normal 130–139
Stage 1 140–159
Stage 2 160–179
Stage 3 180–209
Stage 4 >210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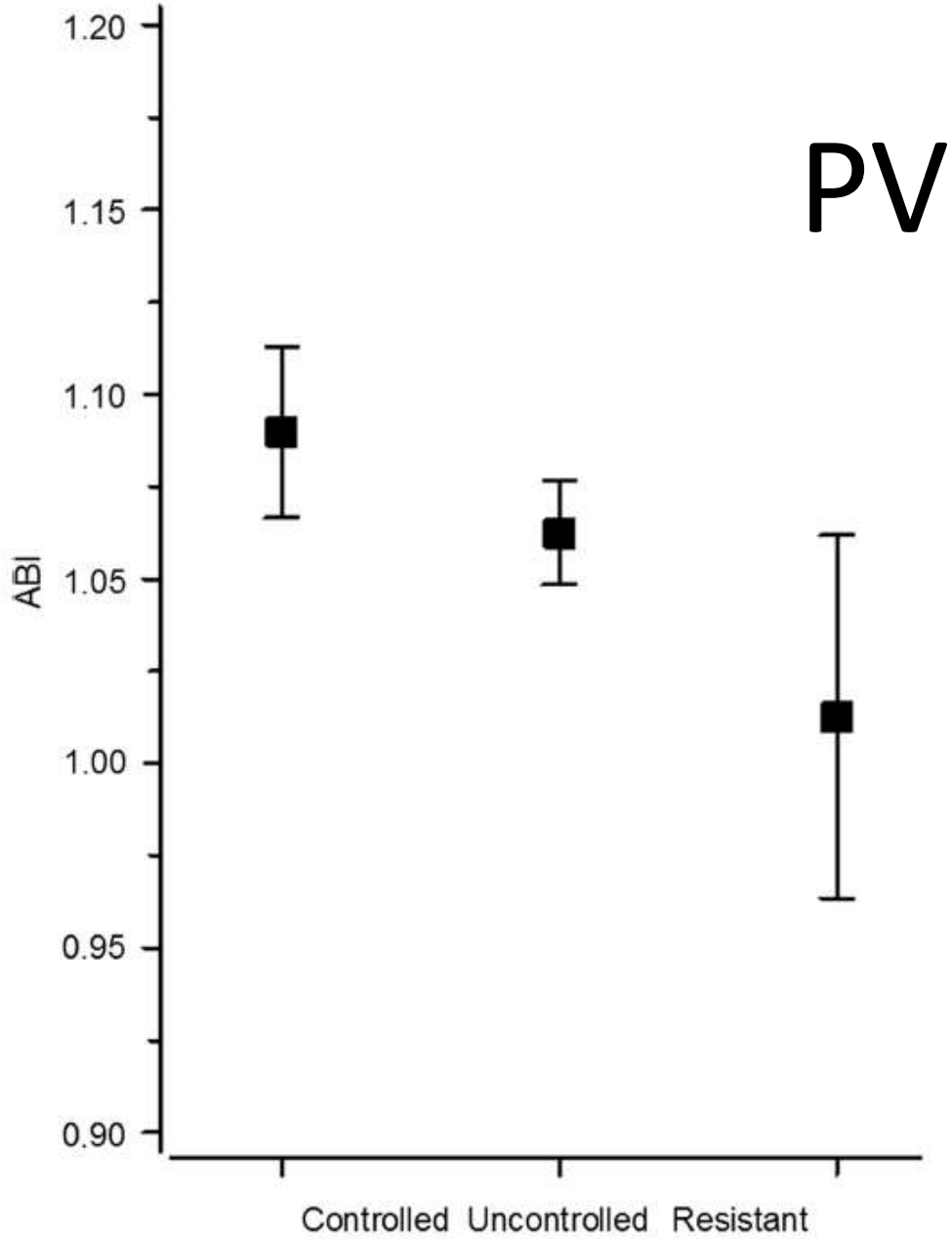
PVD



Korhonen et al., Journal of Human Hypertension (2015) 29, 46–49

Diagnostic Approach

I. Rule out pseudoresistance

II. Confirm (ABPM)

III. Exclude secondary causes

IV. Volume assessment

Diagnostic Approach

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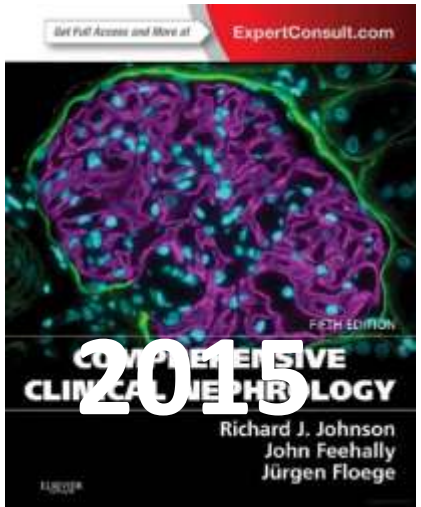
- Proper blood pressure measurement technique
- Check drug adherence
- Exclude any blood Pressure-Increasing Drugs

Pseudoresistance ……

Guidelines for Measurement of Blood Pressure



Patient Factors

Caffeine should not be taken for up to 1 hour before the BP measurement.

Cigarettes should not be smoked for at least 15 minutes before the BP reading.

The standard BP measurement should be made with the patient not talking and seated comfortably, back and arm supported, and legs uncrossed. The cuff must be at the level of the heart, and the arm should be bared.

The urinary bladder should be empty.

On an initial examination, BP should also be checked in the supine position after 5 minutes of rest, in the standing position after 2 minutes, and initially in both arms, especially in patients who are diabetic, older than 65 years, or receiving antihypertensive therapy. Use the higher value if the arms have differing BP readings.

If sequential BP readings are taken in the same position, at least 30 seconds must elapse between BP readings. In patients younger than 30 years, check BP in one leg.

To establish a diagnosis of hypertension, obtain BP readings on three different occasions, at least 1 week apart.

Equipment

The length of the bladder with the cuff should encircle at least 80% of the arm.

The width of the cuff should be equal to two thirds of the distance from the antecubital space to the axilla and should be 40% of the arm circumference. The best cuff for most adults is the 15-cm-wide cuff with a bladder of 33 to 35 cm in length. The distal edge of the cuff should be 2.5 cm (1 inch) above the antecubital fossa. For leg BP, thigh cuff length should encircle 80% of the thigh, and width should be 40% of the thigh circumference. For leg BP, the patient should be prone and popliteal artery sounds measured by auscultation. For automated equipment, the sensor should be over the brachial (or radial or popliteal) artery.

In extremely obese patients, BP may be more accurate when measured in the forearm, palpating and auscultating the radial artery.

For infants, ultrasound equipment may need to be used. The bell of the stethoscope is preferred.

Technique

The initial systolic BP should be checked by palpating the disappearance of the radial or brachial pulse before auscultation, and the cuff then deflated.

The second BP check requires cuff inflation 20 to 30 mm Hg above the palpable systolic level.

Deflate the cuff at a rate of 2 to 4 mm Hg per second.

Record the Korotkoff sound I (appearance of sound) as the systolic BP and record the Korotkoff sound V (silence, 2 mm Hg below the last sound) as the more reproducible diastolic BP. If the sounds do not disappear, record the muffled sound (phase IV) as the diastolic BP.

The sounds may be augmented by the patient raising the arm and opening and closing the hand 10 times before inflating the BP cuff.

Do not stop between systolic and diastolic BP readings; deflate the cuff, wait at least 30 seconds, and then reinflate. On each occasion, record at least two BP readings. If the BP readings vary by more than 5 mm Hg, take additional BP readings until two are within 5 mm Hg.

In children, the same standards apply for cuff size; Korotkoff sound V should be used. If the child is uncooperative, the systolic BP may be determined by palpation.

Pseudoresistance ……

Check drug adherence

Journal of Human Hypertension (2007) 21, 579–584

www.nature.com/jhh

ORIGINAL ARTICLE

Validity of four indirect methods to measure adherence in primary care hypertensives

JC Prado Jr[1,5], E Kupek[2] and D Mion Jr[3,4]

[1]Department of Public Health, CCS/UFSC, Campus Universitário, Trindade, Florianópolis, Santa Catarina, Brazil; [2]Department of Public Health – CCS/UFSC, Federal University at Santa Catarina, Campus Universitário, Trindade, Florianópolis, Santa Catarina, Brazil; [3]Hypertension Unit, Clinic Hospital, University of São Paulo, São Paulo, Brazil; [4]Department of Nephrology, School of Medicine, University of São Paulo, São Paulo, Brazil and [5]Municipal Secretary of Health, Florianópolis, Santa Catarina, Brazil

- Percentage of pills remaining in the bottle: Use 80–110% (Gold standard)
- Degree of BP control on the second visit
- Knowledge about BP medication
- Self-report on adherence

- Morisky–Green test:
  - Attitude of the patients in relation to their medication
  - 4 questions to be answered with ‘yes’ or ‘no’:

    (1) Have you ever forgotten to take your medicine?

    (2) Are you not careful about taking your medicine?

    (3) When you feel better, do you sometimes stop taking your medicine?

    (4) At times, if you feel worse when you take your medicine, do you stop taking them?

Pseudoresistance ……

Exclude Blood Pressure-Increasing Drugs

Nonnarcotic analgesics
Nonsteroidal antiinflammatory agents, including aspirin
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

Muxfeldt et al., Journal of Human Hypertension. 2013;27:657–662

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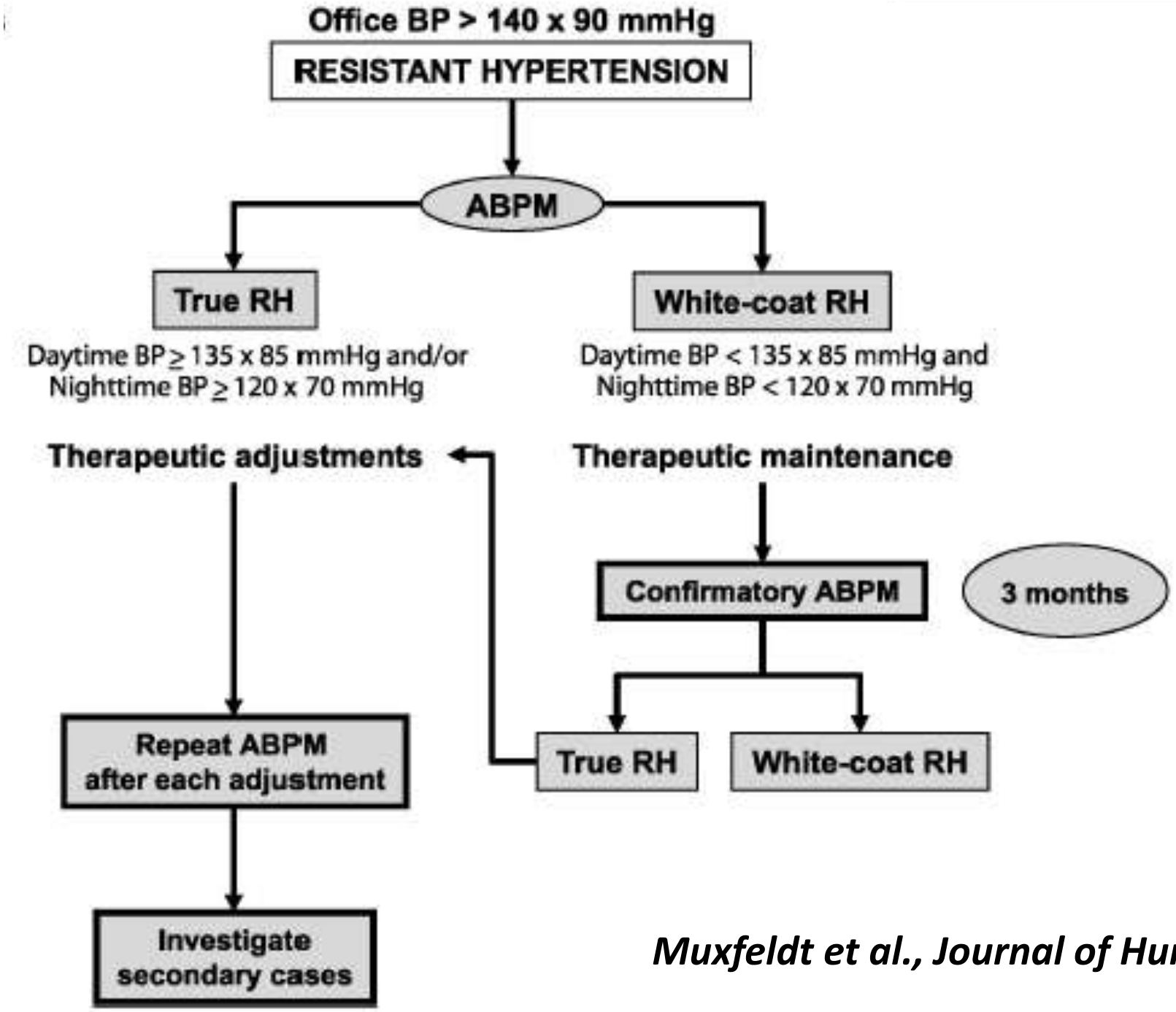

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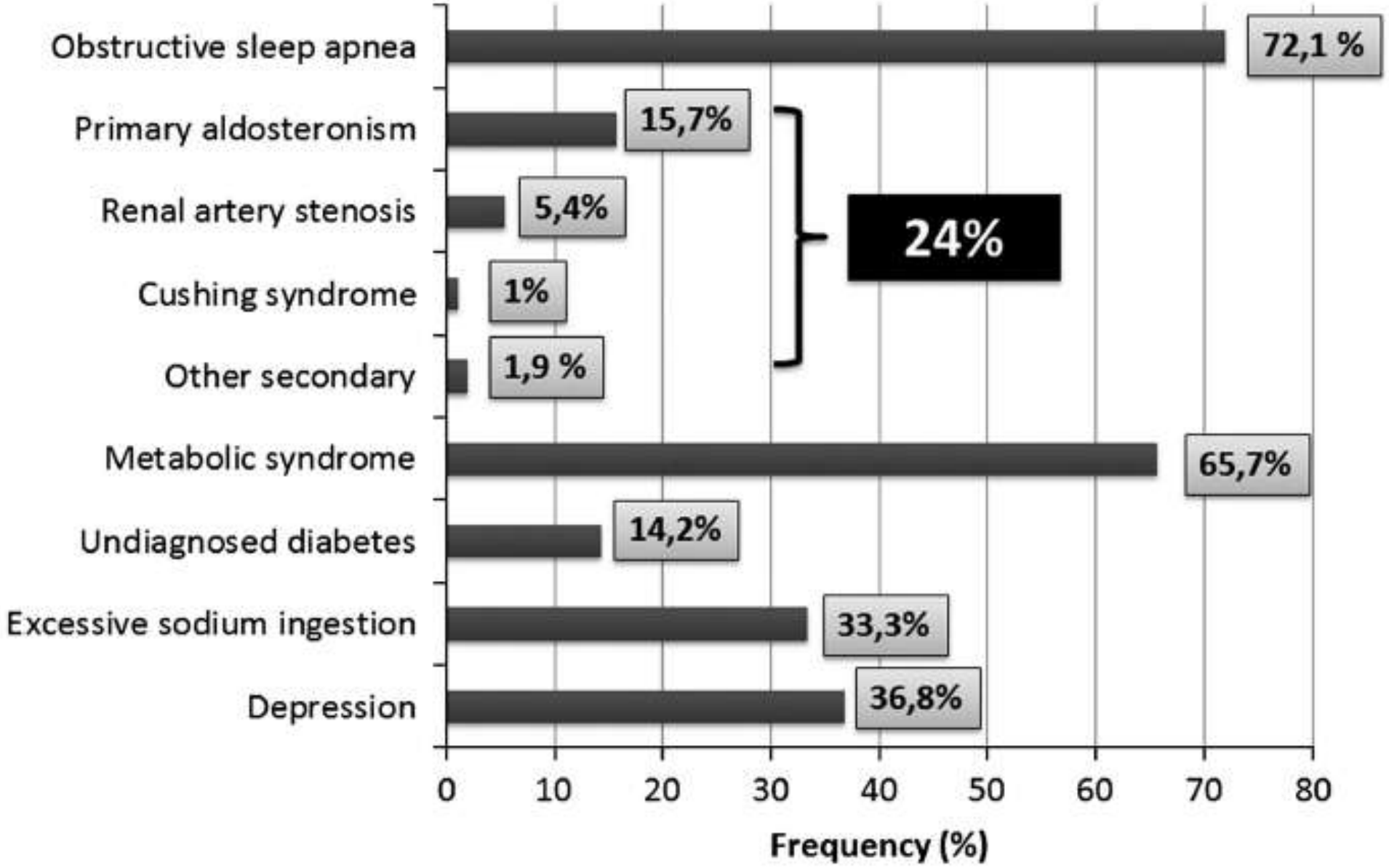

Florczak et al., Journal of Human Hypertension (2013) 27, 678–685

Sleep apnea:

Symptoms: diurnal somnolence, fatigue and snoring

Signs: high BMI, high neck circumference

Polysomnography: gold standard

Diagnostic: apnea-hypopnea index: > 5 and ≤ 15 (mild) , > 15 and ≤ 30 (moderate), > 30 (severe)

Hyperaldosteronism:

1) Screening: Serum aldosterone / plasma renin ratio (ARR)
   Maintenance of anti-hypertensive except spironolactone (discontinue 6 weeks before)
   False positive: betablockers, clonidine / False negative: RAAS blockers and diuretics
2) ARR > 30 and Aldosterone > 15 ng/dL: positive screening
3) Confirmatory tests: fludrocortisone suppression, saline infusion or high dietary salt loading
4) Helicoidal CT of adrenals: unilateral findings
5) Adrenal venous samples proving lateralization of aldosterone secretion:
6) Positive lateralization adenoma: surgical treatment
   No lateralization or adrenal hyperplasia MR blockers

Renal artery stenosis:

Renal scintilography (with/without captopril) – better evaluation of functional significance of renal artery lesion, except for patients with severe CKD

Doppler ultrasonography – easily performed but obesity may be a limitation

CT angiography – high sensitivity and specificity, but is recommended only in patients with serum creatinine < 3.0mg/dL (requires iodinated contrast media)

Magnetic resonance angiography – high sensitivity and specificity for stenosis > 50%

Digital subtraction angiography – gold standard

Conventional angiography – anatomic diagnosis without hemodynamic evaluation

Muxfeldt et al., Journal of Human Hypertension. 2013;27:657–662

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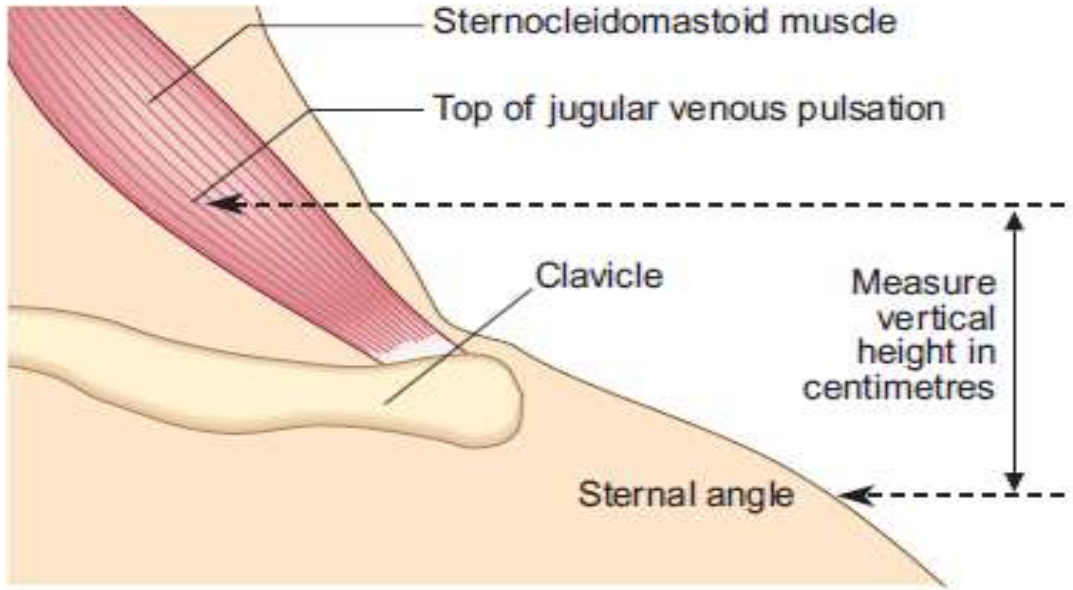
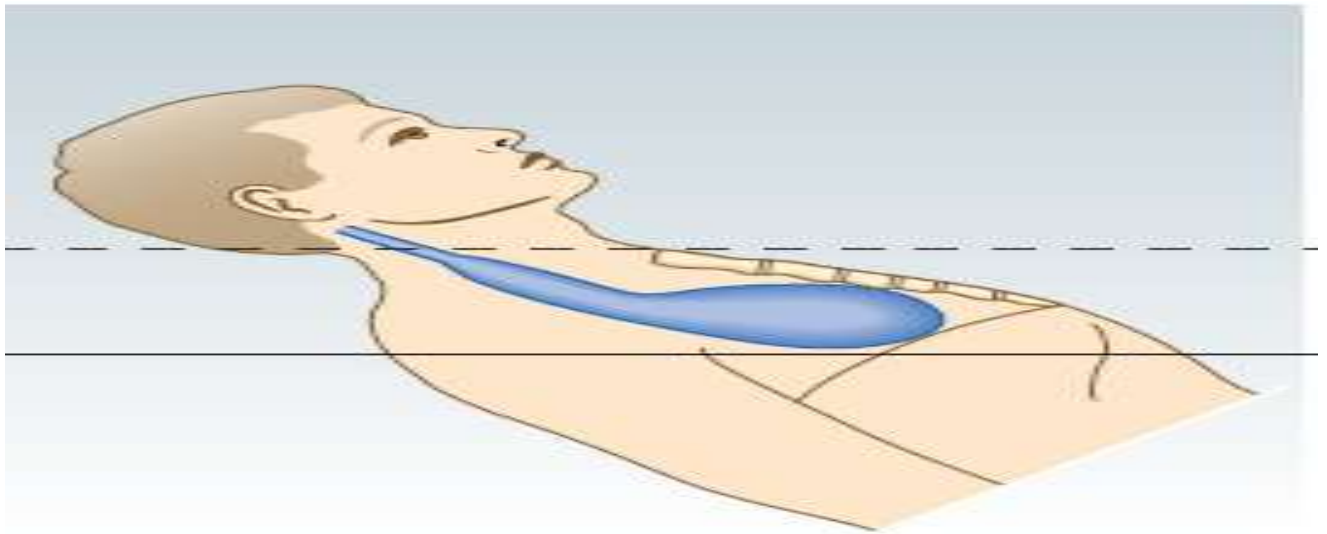
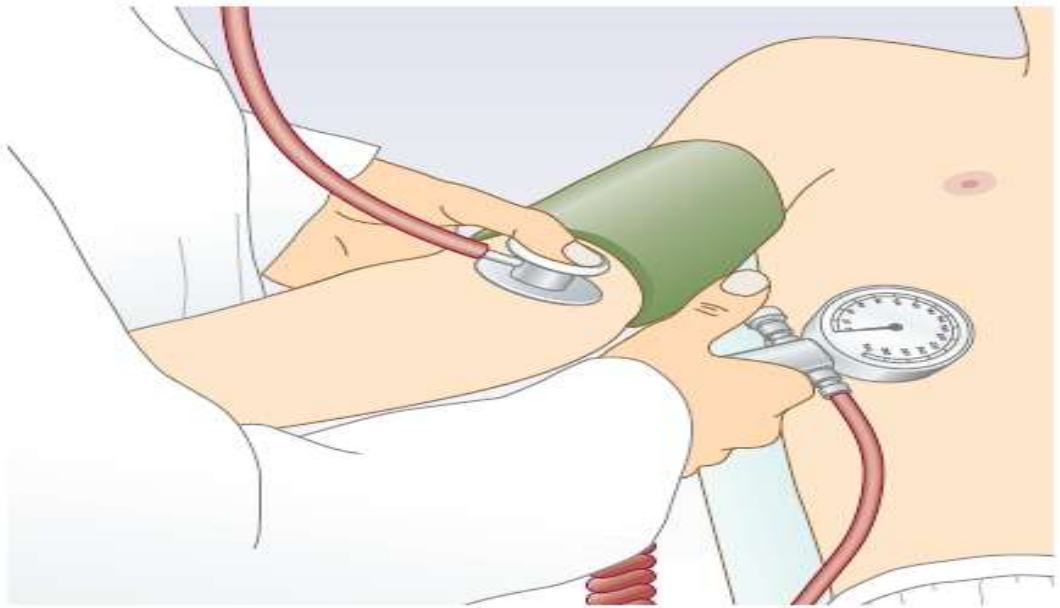
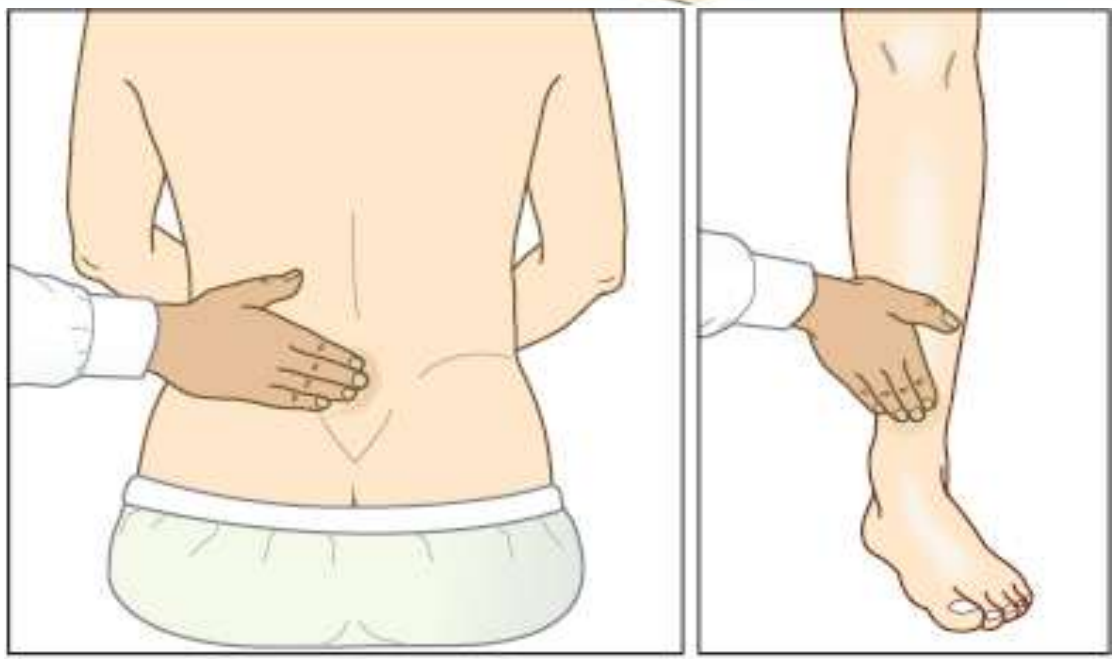
Clinical assessment





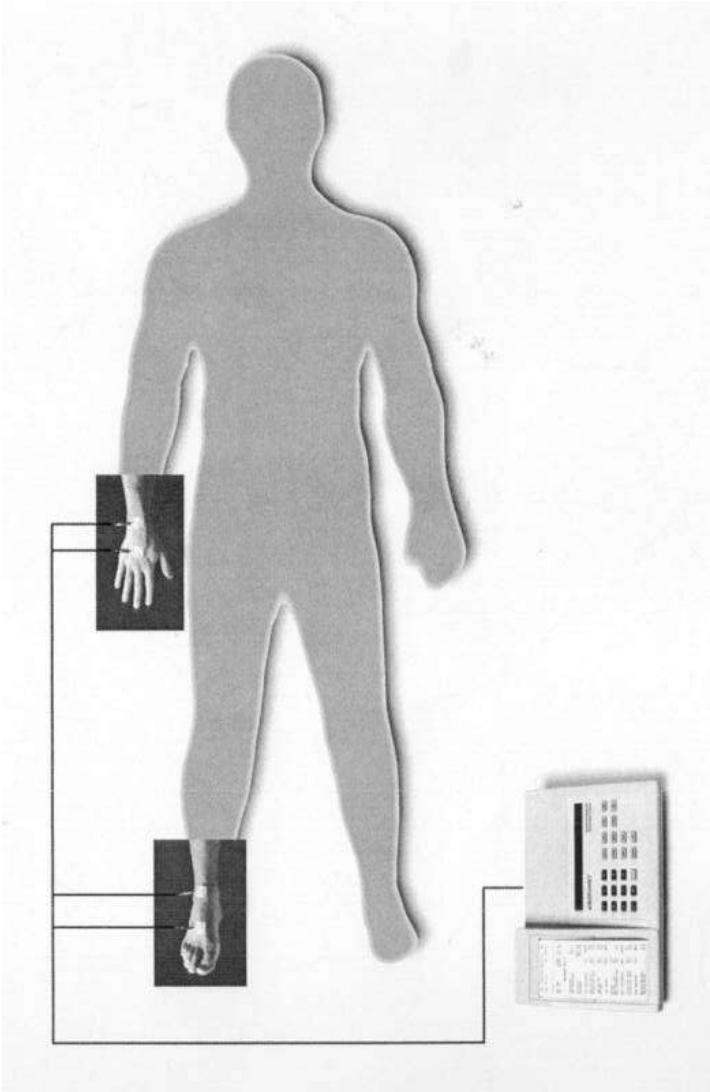




- Plasma renin activity, BNP and NT-pro-BNP levels.

- Echocardiography: time-consuming and requires specialized equipment and personnel

- Bioimpedance:
  - Noninvasive, reliable and simple bedside technology
  - Diagnoses subclinical fluid accumulation



Treatment

I. Appropriate Lifestyle changes

II. Adequate Antihypertensive Scheme

- A. Timing (Chronotherapy)
- B. Type

III. New Drugs

IV. Interventional Therapies

Treatment

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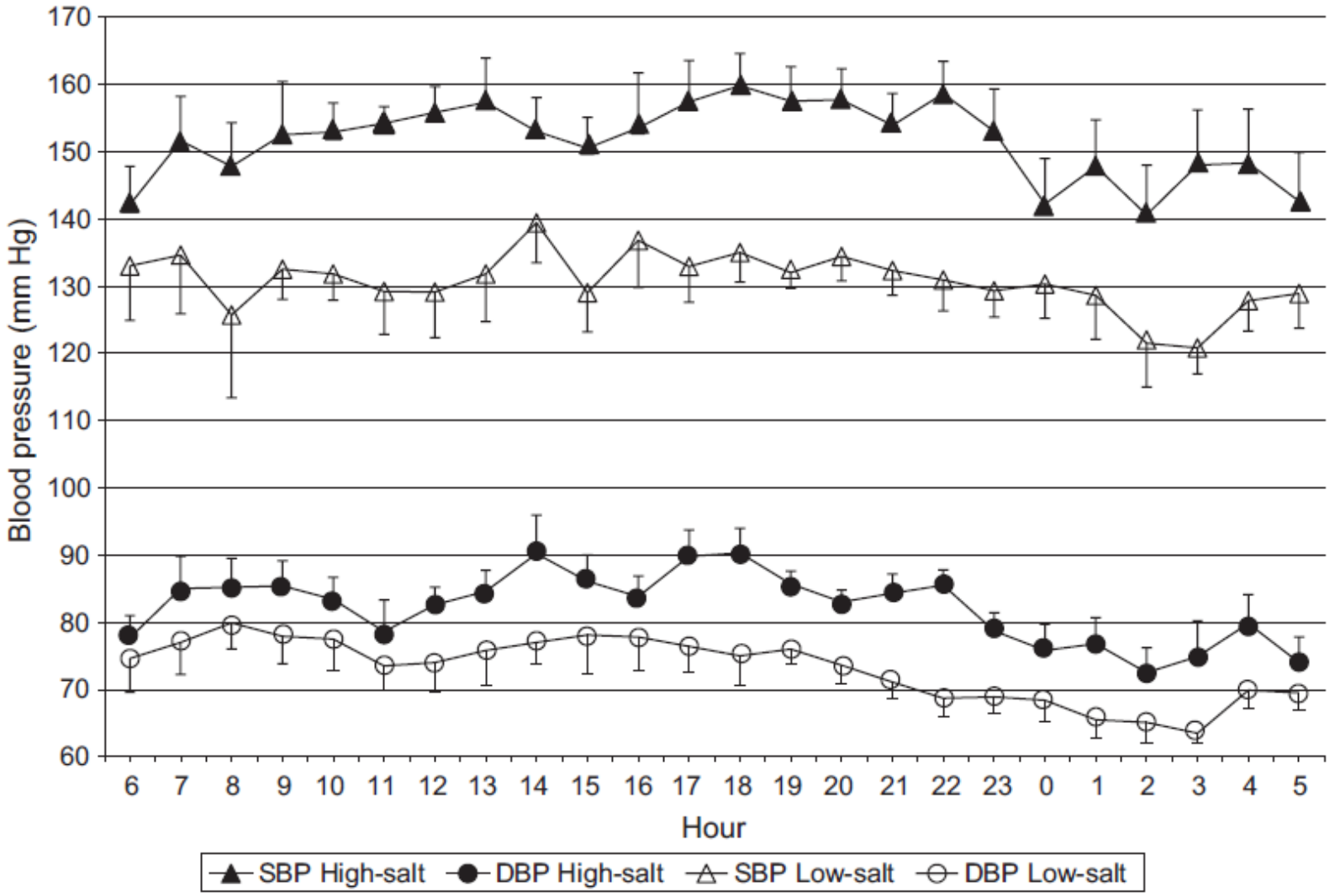
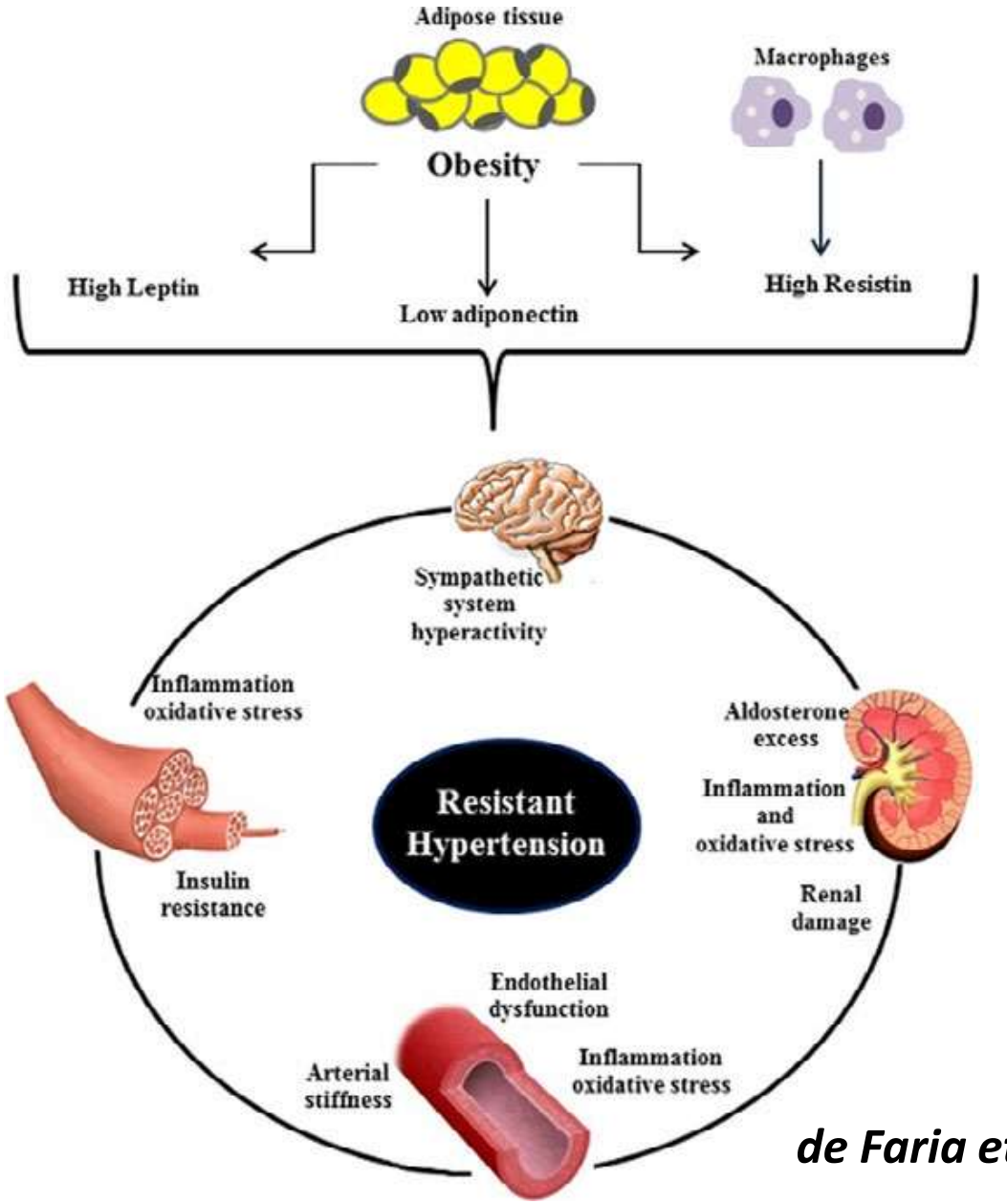
A. Low Salt Intake



Pimenta et al., Hypertension. 2009;54:475-481.

B. Weight Loss & Physical Activity



de Faria et al., The Journal of Clinical HypertensionVol 2014;16(10): 754-9.

Treatment

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A. Timing (Chronotherapy)

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Treatment of Hypertension With Chronotherapy: Is It Time?

Annals of Pharmacotherapy
1–12

DOI: 10.1177/1060028014563535
aop.sagepub.com
SAGE

Paul M. Stranges, PharmD[1,2], Amy M. Drew, PharmD[1,3], Patricia Rafferty, PharmD[1,4], Jerrica E. Shuster, PharmD[1,2], and Amie D. Brooks, PharmD[1,4]

Population (n)	Follow-up (Mean)	Baseline 48-Hour BP, Mean	Awake-BP Reduction		Asleep-BP Reduction		Percentage Nondipper		Composite CVD Outcome[a] (%)		Reference
			Morning Admin	Bedtime Admin	Morning Admin	Bedtime Admin	Morning Admin	Bedtime Admin	Morning Admin	Bedtime Admin	
Essential HTN (2201)	5.6 Years	130.6/78.5	9.4/7.2	8.9/6.5	6.6/5.2	11.8[b]/7.9[b]	61.6	34.4[b]	17.2	6.3[b]	Hermida et al[6]
Type 2 diabetes (448)	5.4 Years	133.4/74.3	8.3/6.1	9.1/6.3	6.1/4.6	14.2[b]/9.1[b]	76.3	49.5[b]	29.3	10.6[b]	Hermida et al[7]
CKD (661)	5.4 Years	134.7/78.4	9.4/6.9	8.1/5.7[b]	6.4/4.9	12.0[b]/7.8	71.1	41.0[b]	31.3	10.6[b]	Hermida et al[8]
Resistant HTN (776)	5.4 Years	130/74.7	5.4/4.2	7.3/5.1	2.7/2.5	12.6[b]/7.8[b]	74.7	39.2[b]	26	10.6[b]	Ayala et al[22]

Advisory Document/ Guideline (Year)	Chronotherapy	Reference
JNC8 (2013)	Not addressed	James et al[14]
JNC7 (2003)	Not addressed	Chobanian et al[15]
AHA/ACC/CDC (2013)	Not addressed	Go et al[16]
ESH/ESC (2013)	Not addressed	Mancia et al[17]
ASH/ISH (2014)	Not Addressed	Weber et al[18]
CHEP (2013)	Consider to target asleep-BP decrease ≥10%	Lindsay et al[19]
ABPM (2013)	Consider to enhance control of asleep-BP or normalize dipping status	Hermida et al[13]
NKF/KDIGO (2012)	Not addressed	Improving Global Outcomes [88]
ADA (2014)	Recommend ≥1 antihypertensive dosed at bedtime	American Diabetes Association[89]
AHA (2008)	Consider to improve overnight BP control or adherence	Calhoun et al[90]

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First 3 drugs

Diuretics: volume retention

Thiazides: chlorthalidone preferentially. Also hydrochlorothiazide or indapamide

Loop diuretics: Creatinine clearance < 30 ml/min

2 other drugs: reduces CV morbidity and mortality

ACEi/ARB, calcium channel blocker, beta-blocker

ACEi and ARB: prevention/regression subclinical organ damage (LVH and microalbuminuria)

Beta-blocker: care in patients with obesity and metabolic syndrome

Muxfeldt et al., Journal of Human Hypertension. 2013;27:657–662

Fourth drug **Spironolactone**

Initial dose: 25-50 mg/day. Higher doses may be necessary in hyperaldosteronism (where plasma renin may be useful to check completeness of MR blockade)

Serum creatinine and potassium should be monitored

Plasma aldosterone and renin are not usually necessary

Other drugs **Direct vasodilators:** hydralazine and minoxidil – take care with fluid retention

Centrally-acting 2 adrenergic agonist: clonidine

Frequently it is necessary to combine two diuretics (thiazides and loop diuretics)

Muxfeldt et al., Journal of Human Hypertension. 2013;27:657–662

Aldosterone Antagonists

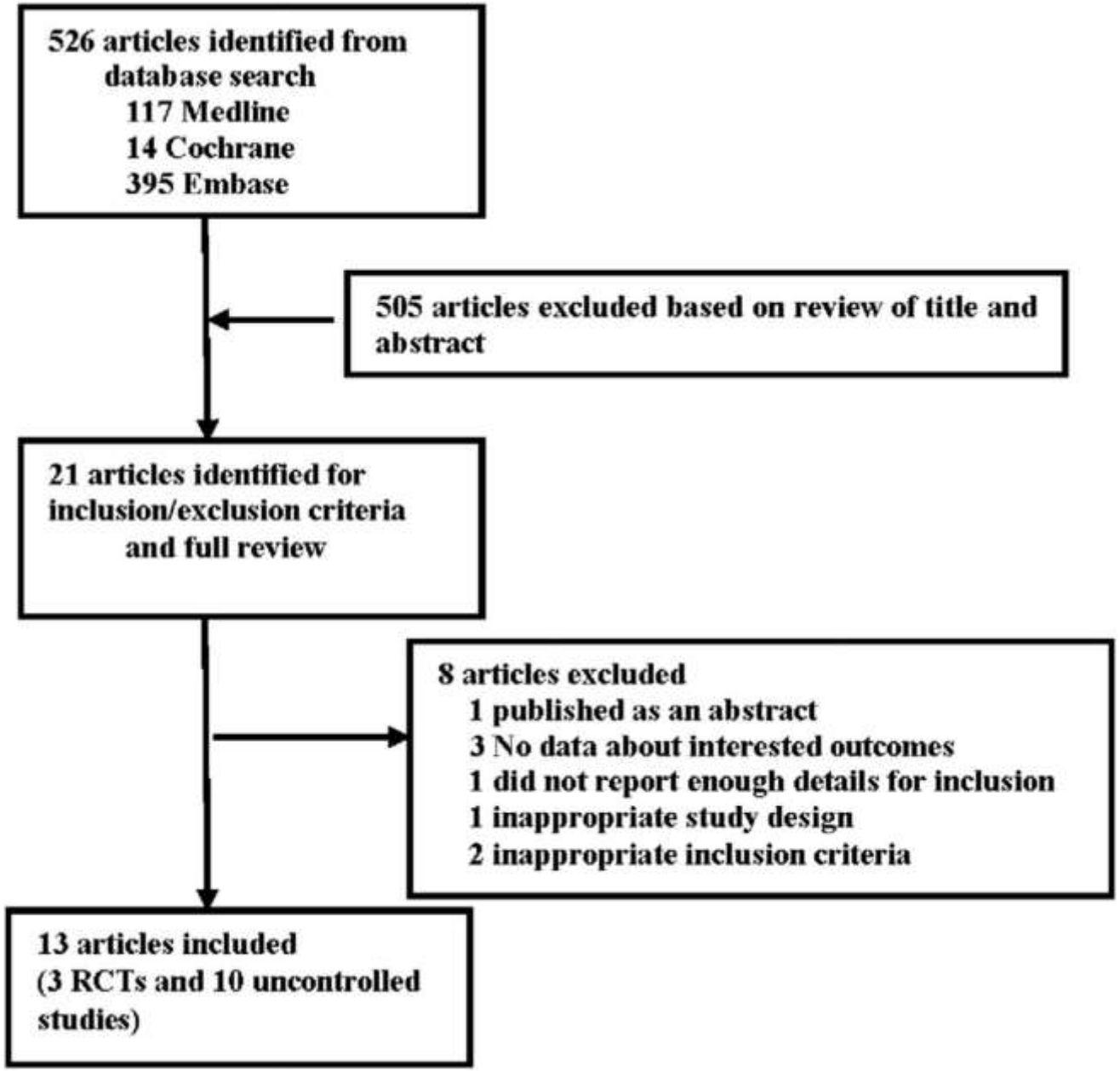
Journal of Human Hypertension (2014), 1–8

www.nature.com/jhh

ORIGINAL ARTICLE

Effect of aldosterone antagonists on blood pressure in patients with resistant hypertension: a meta-analysis

G Liu, X-X Zheng, Y-L Xu, J Lu, R-T Hui and X-H Huang

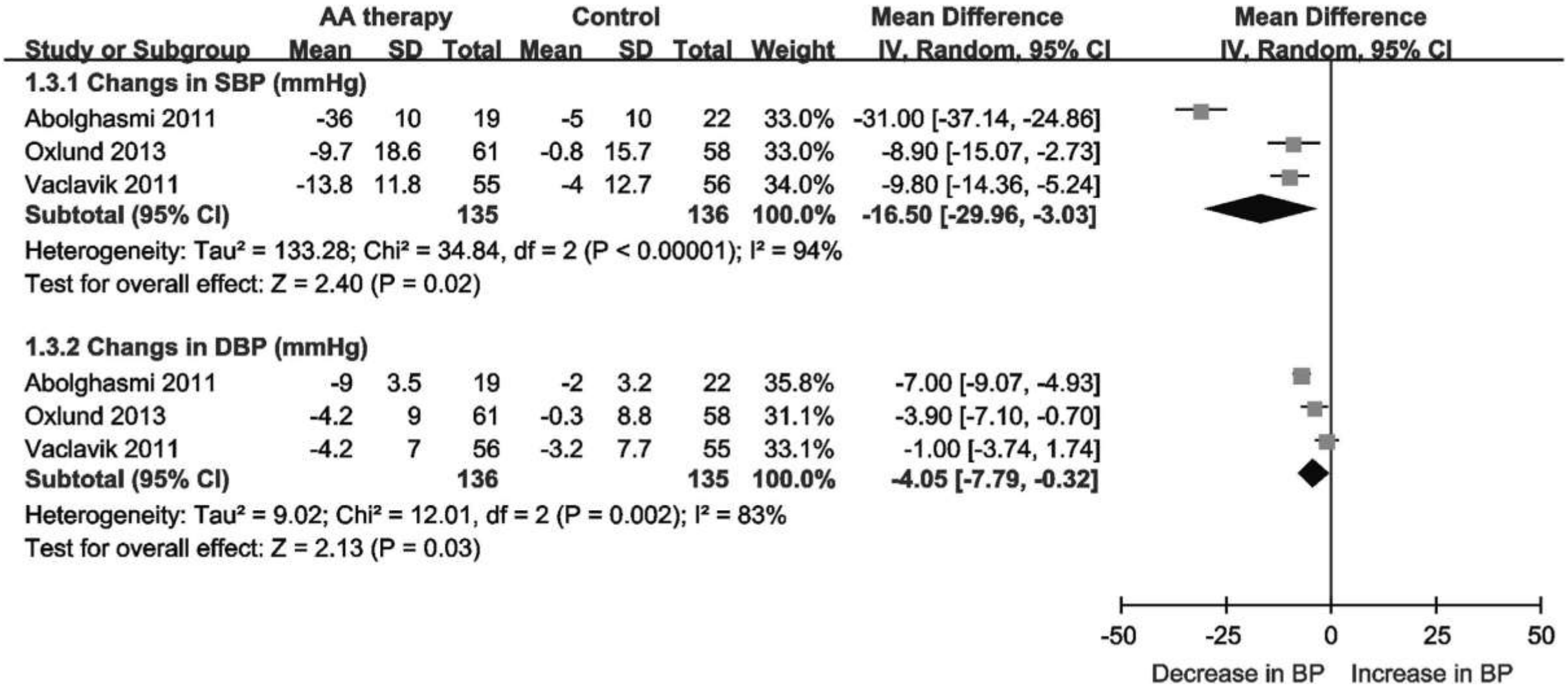


Liu et al., Journal of Human Hypertension (2014), 1–8

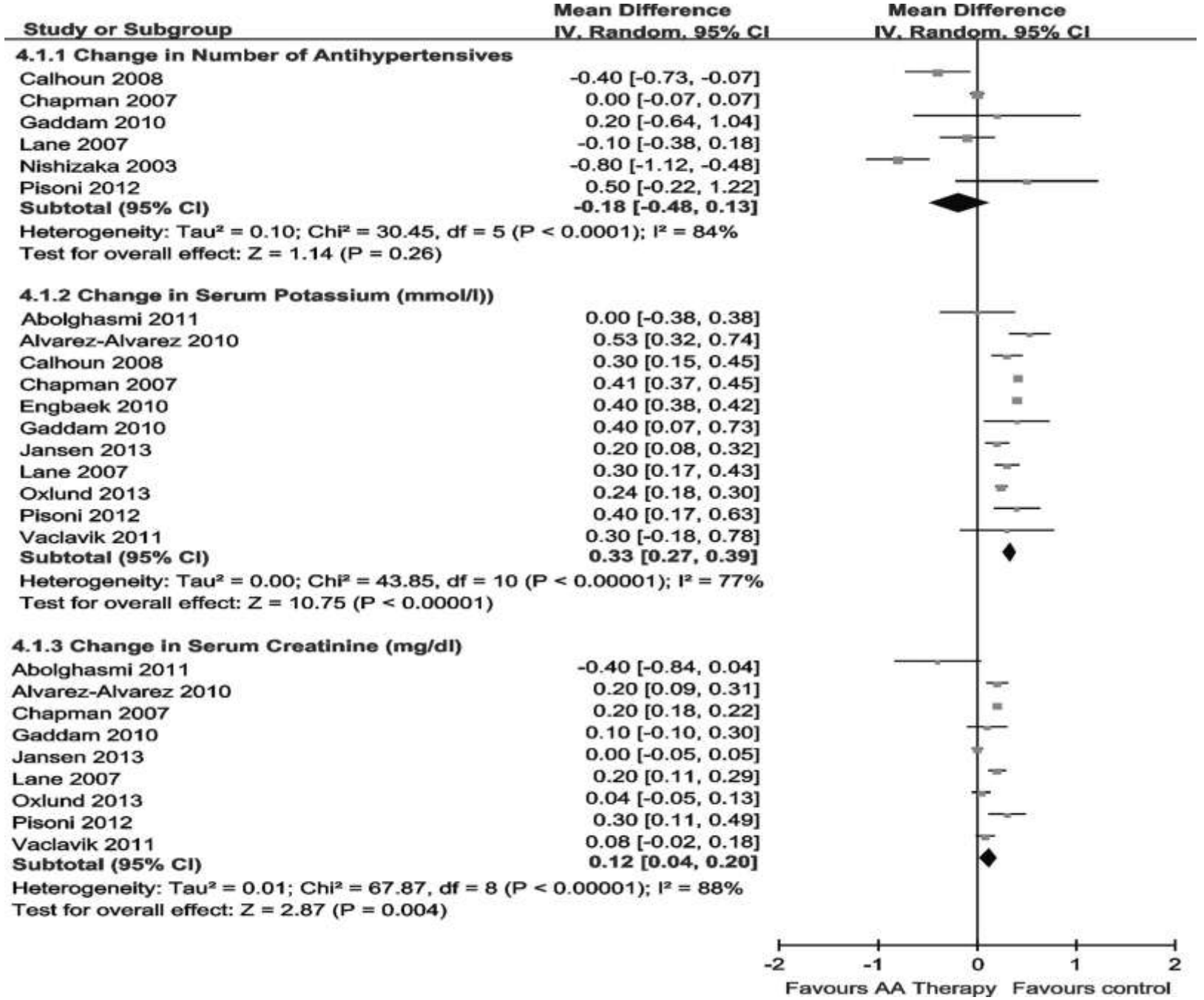
Patients Characteristics

Study	Treatment Group	Age (years)	Male (%)	BMI (kg m^{-2})	CKD (%)	PA (%)	Baseline BP (mm Hg)
Abolghasmi *et al.*[12]	Spironolactone	49 ± 13.2	53	31.2 ± 4.3	100	0	171 ± 10/95 ± 4
	Control	50 ± 10.1	55	30.0 ± 3.2	100	0	170 ± 10/93 ± 5
Vaclavik *et al.*[13]	Spironolactone	61.4 ± 9.6	67	32.3 ± 5.1	0	15	143 ± 13.5/81 ± 10.2
	Placebo	60.1 ± 9.4	57	32.3 ± 5.3	0	16	140 ± 16.4/79 ± 10.2
Oxlund *et al.*[14]	Spironolactone	62.9 ± 7.1	75	32.0	0	0	144 ± 9/78 ± 7
	Placebo	63.9 ± 6.9	78	31.5	0	0	143 ± 11/78 ± 7
Nishizaka *et al.*[16]	Spironolactone	55 ± 12	41	33.6 ± 8.7	0	45	163 ± 18/91 ± 14
Lane *et al.*[17]	Spironolactone	62.5 ± 12.1	31.9	NR	0	0	182 ± 23.2/93 ± 14.5
Chapman *et al.*[18]	Spironolactone	63 ± 8	77	29.4 ± 4.6	0	0	157 ± 18/85 ± 11.5
Calhoun and White[6]	Eplerenone	62 ± 10	70	32.1 ± 5.5	0	4	150 ± 14.5/79 ± 12.5
Engbaek *et al.*[20]	Spironolactone	62.2 ± 12.8	45	NR	0	0	169 ± 21.3/88 ± 12.8
de Souza *et al.*[21]	Spironolactone	62 ± 10	27.6	30.2 ± 5.1	0	0	149 ± 14/86 ± 11
Alvarez-Alvarez *et al.*[22]	Spironolactone	66.9 ± 8.8	50	31.8 ± 3.94	0	0	141 ± 14.4/78 ± 9.1
Gaddam *et al.*[23]	Spironolactone	56.5 ± 6.5	58	36.8 ± 6.8	0	0	147 ± 13/82 ± 14
Pisoni *et al.*[24]	Spironolactone or Eplerenone	63 ± 11	64	31.5 ± 6.4	100	0	162 ± 22/87 ± 17
Jansen *et al.*[15]	Eplerenone	50.5 ± 6.6	56.4	28.8	0	0	150 ± 17.8/92 ± 10.9

Liu et al., Journal of Human Hypertension (2014), 1–8



Liu et al., Journal of Human Hypertension (2014), 1–8



Liu et al., Journal of Human Hypertension (2014), 1–8

Mechanisms

Targeting of pressor mechanisms not antagonized by other antihypertensive drugs
Counteraction of the secondary hyperaldosteronism triggered by medications (e.g., diuretics)
Decrease of vascular stiffness
Decrease of vascular tone
Improvement of endothelial function
More complete blockade of Na^+ reabsorption along the nephron (e.g., more effective natriuresis)
Individual and/or racial hypersensitivity to MRA
Relative hyperaldosteronism in patients with the metabolic syndrome (e.g., secondary to overweight-obesity)
Unidentified primary aldosteronism

Rossi et al., Hypertension Research (2014) 37, 1029–1031

Treatment

I. Appropriate Lifestyle changes

II. Adequate Antihypertensive Scheme

- A. Timing (Chronotherapy)
- B. Type

III. New Drugs

IV. Interventional Therapies

- NEP inhibitors (Omapatrilat, others—compassionate use)
- Newer aldosterone receptor antagonists (Eplerenone)
- Aldosterone synthase inhibitors
- Extended release clonidine
- Endothelin receptor antagonists
- New formulations or new combinations of different classes of agents

Laurent et al., Lancet 2012; 380: 591–600

Treatment

I. Appropriate Lifestyle changes

II. Adequate Antihypertensive Scheme

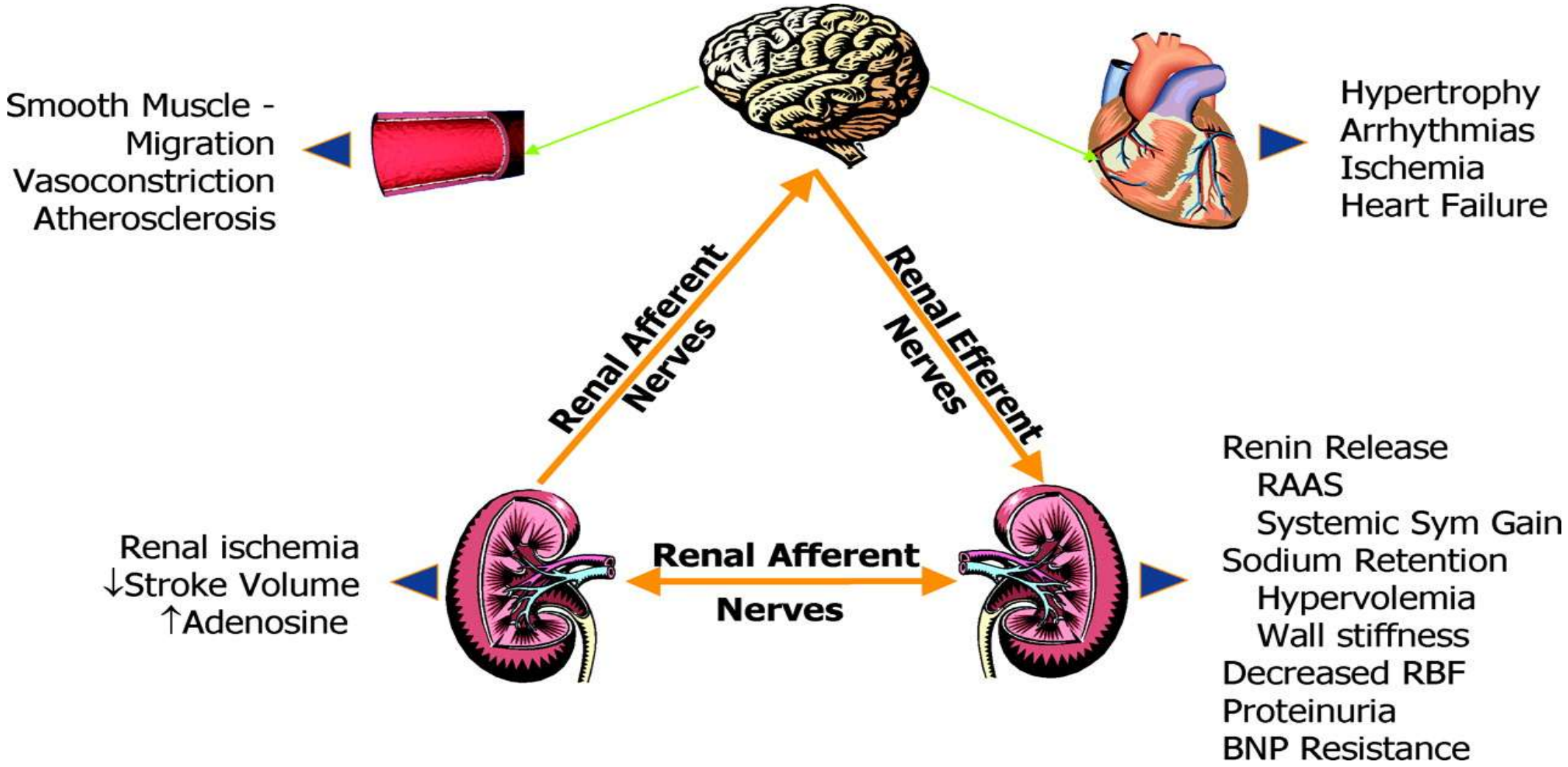
A. Timing (Chronotherapy)

B. Type

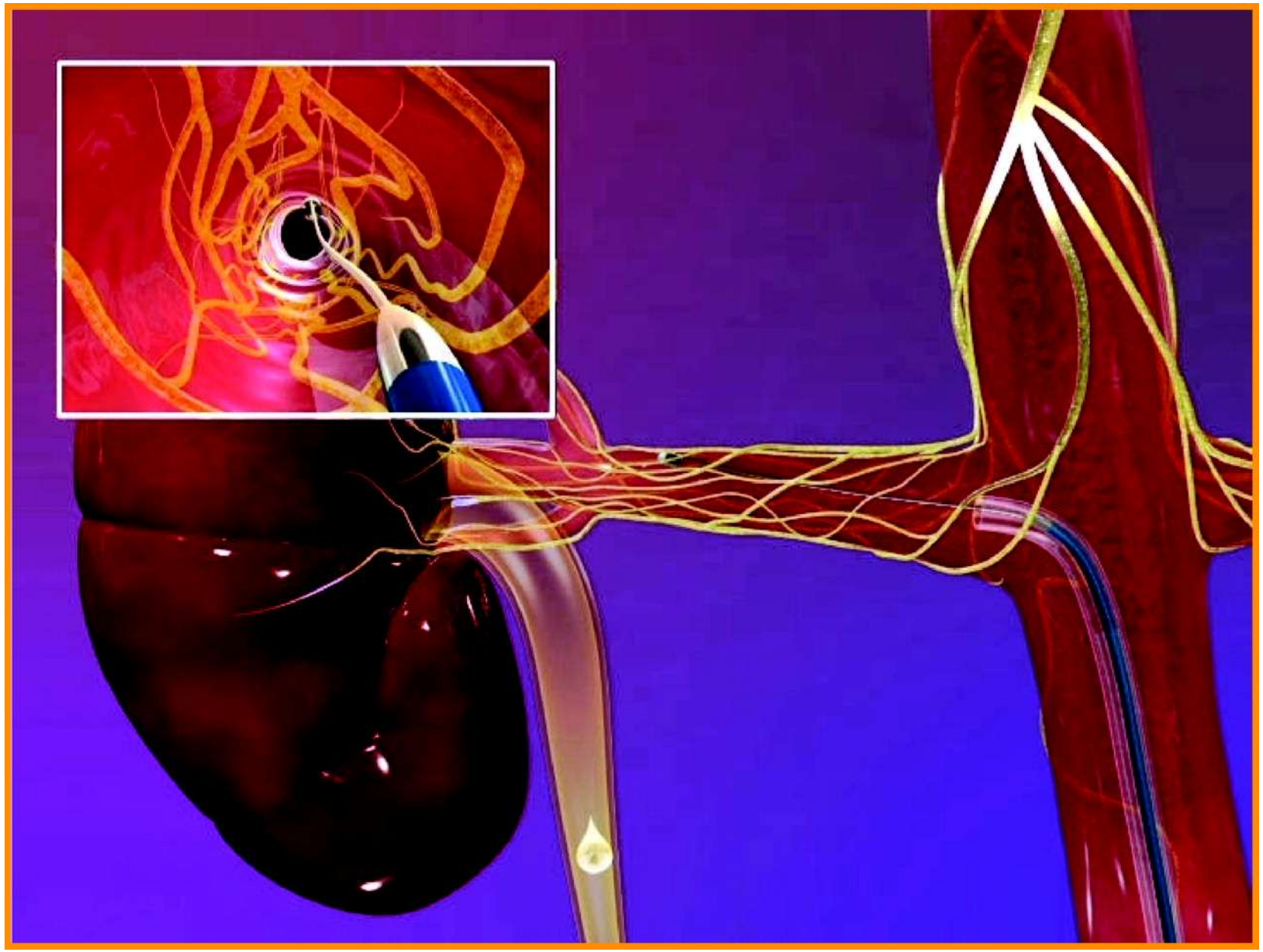
III. New Drugs

IV. Interventional Therapies

1. Renal Sympathetic Denervation

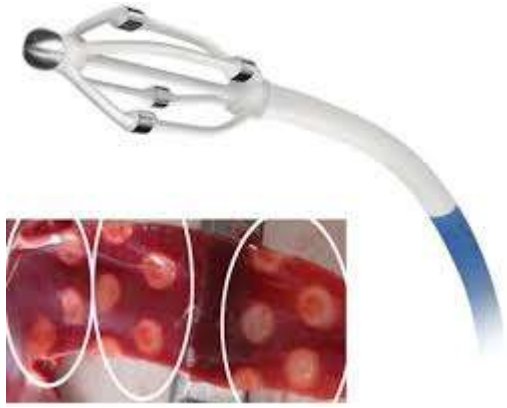


Krum H et al. Circulation 2011;123:209-215

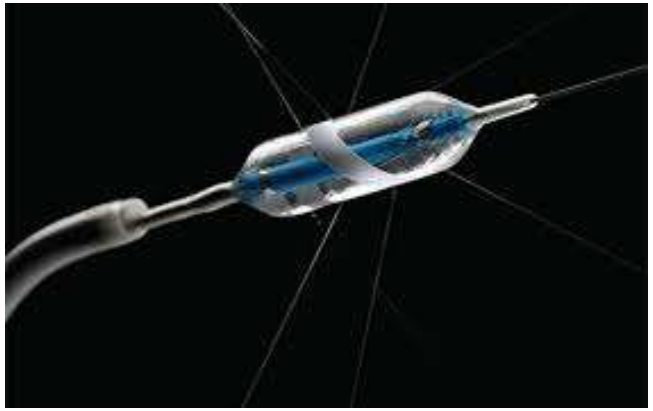


Krum H et al. Circulation 2011;123:209-215

Medtronic simplicity



ENLIG/HTN St Jude

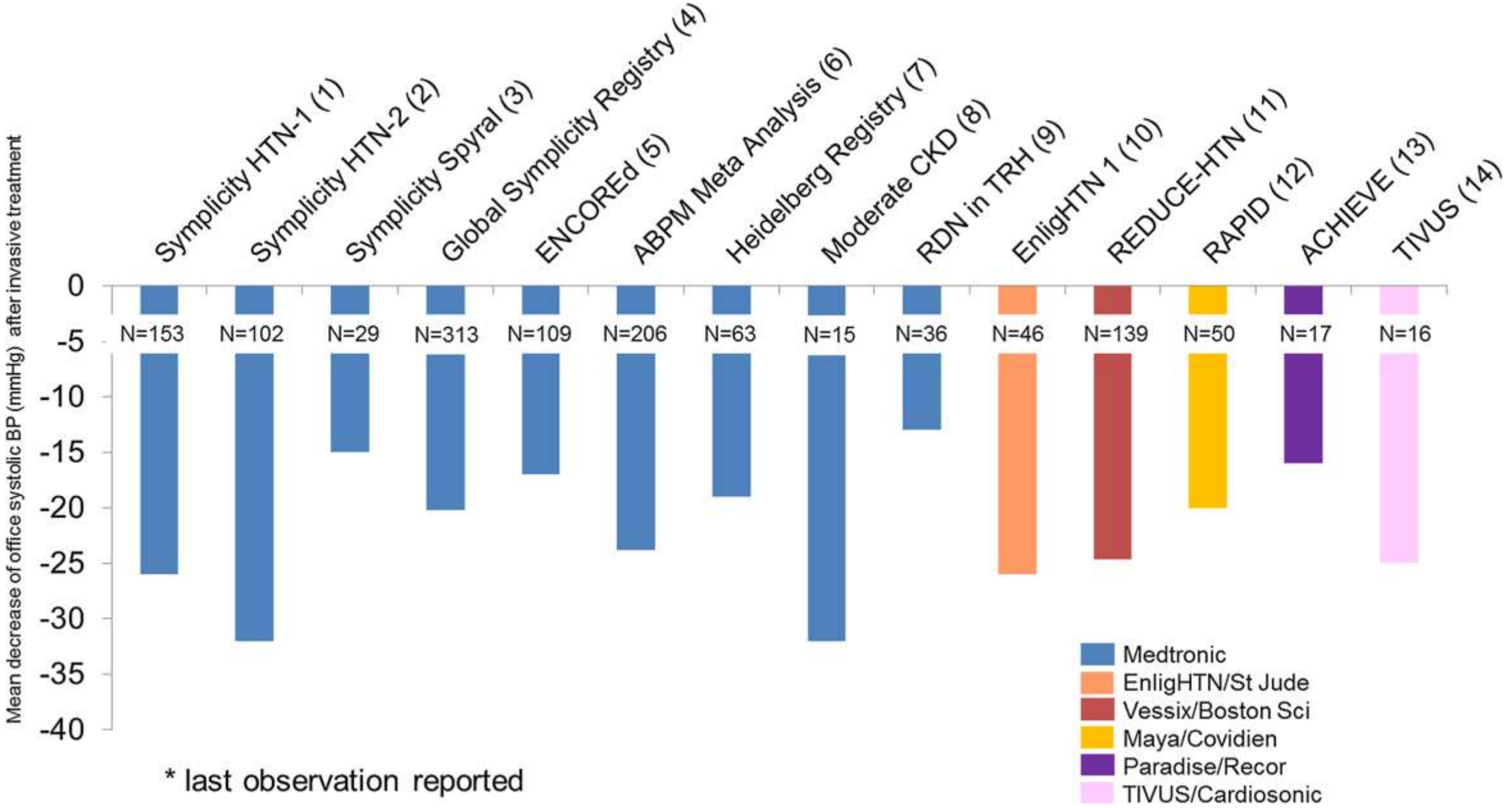


Maya Covidien

Vessix/Boston Sci

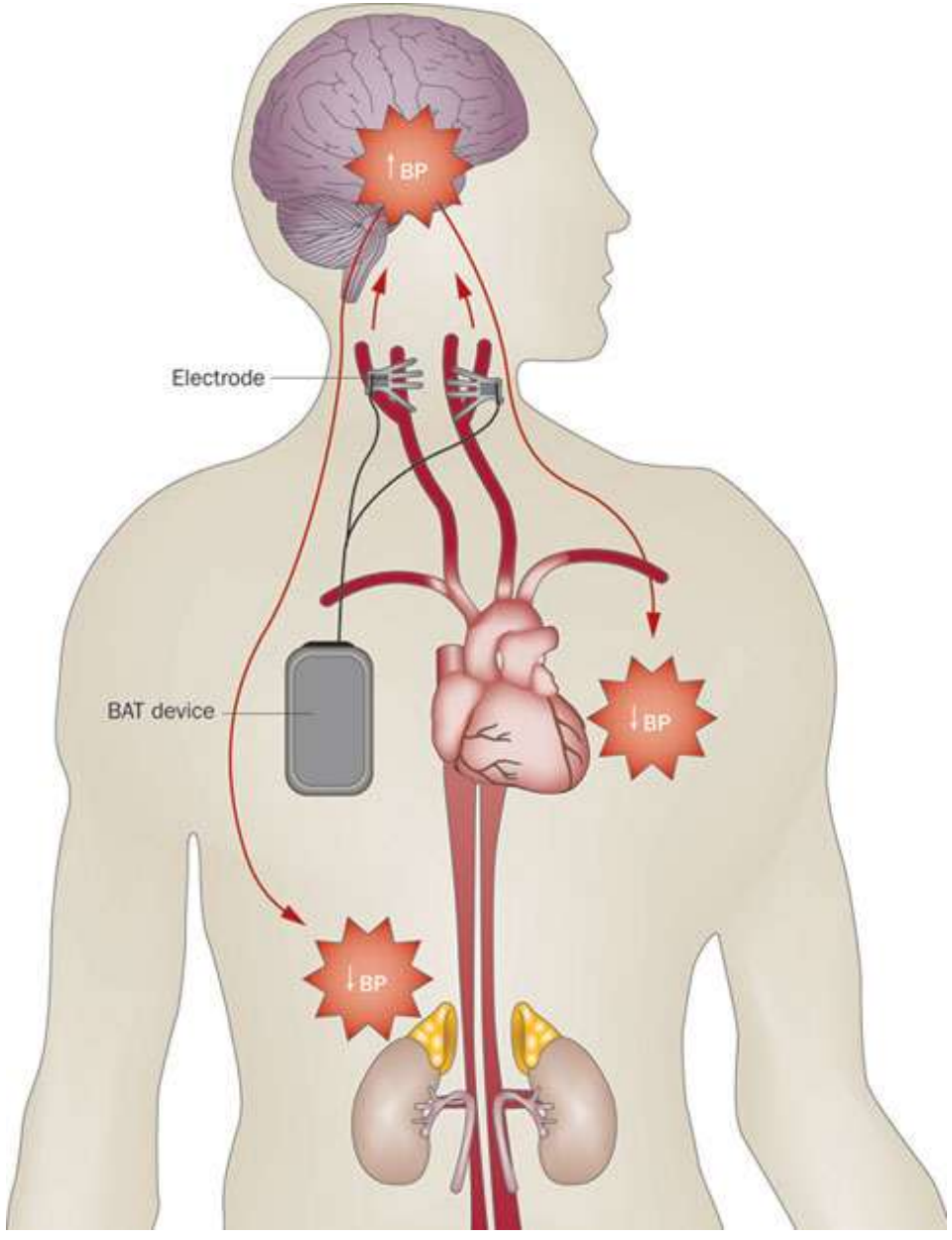
Paradise Recor

TIVUS/Cardiosonic



Ott et al., Curr Hypertens Rep (2014) 16:488

2. Baroreceptor activation therapy (BAT)



Rheos System, CVRx

Paulis, L. et al., Nat Rev Cardiol 2012

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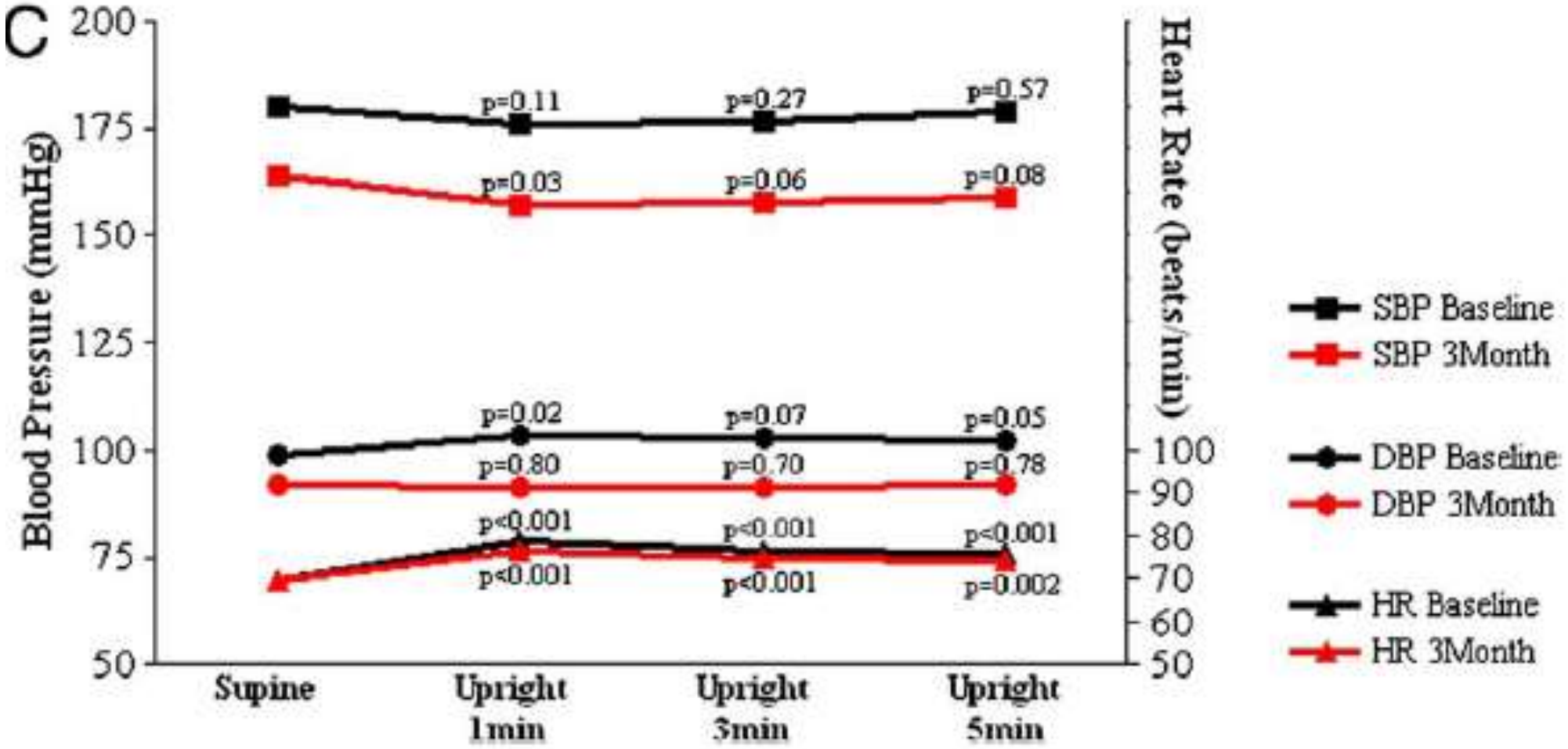
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.03.089

Hypertension

Novel Baroreflex Activation Therapy in Resistant Hypertension

Results of a European Multi-Center Feasibility Study

Device-Based Therapy in Hypertension (DEBuT-HT) trial – 42 Patients



Scheffers, et al., J Coll Am Cardiol. 2010;56(15):1254–8

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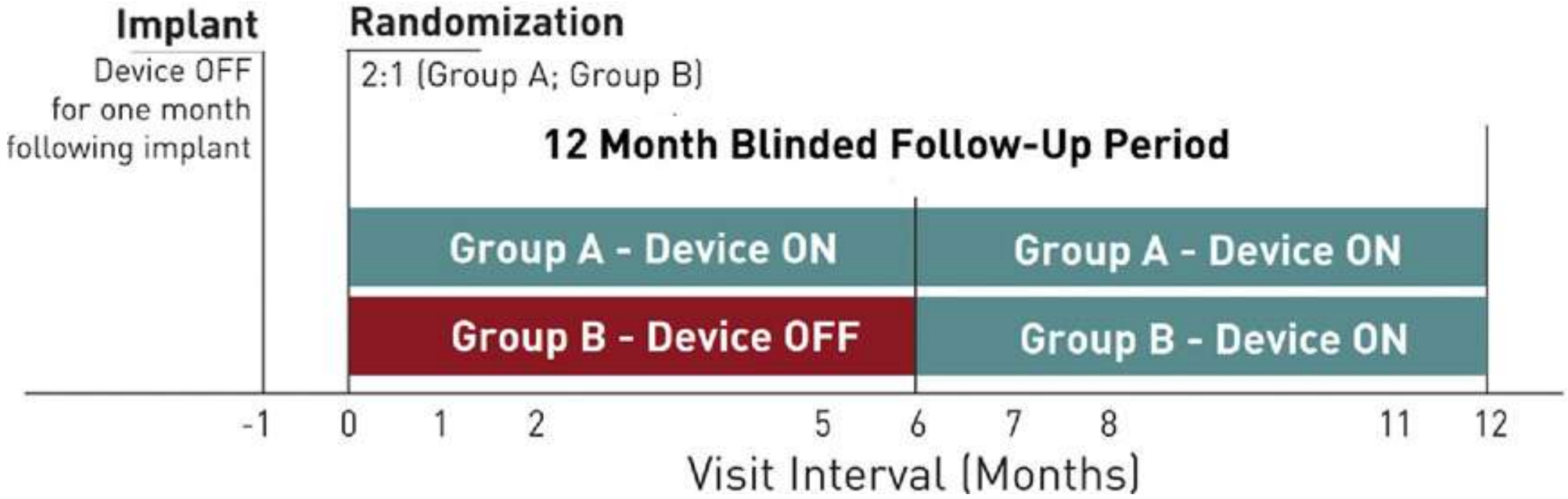
Vol. 58, No. 7, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.008

EXPEDITED PUBLICATION

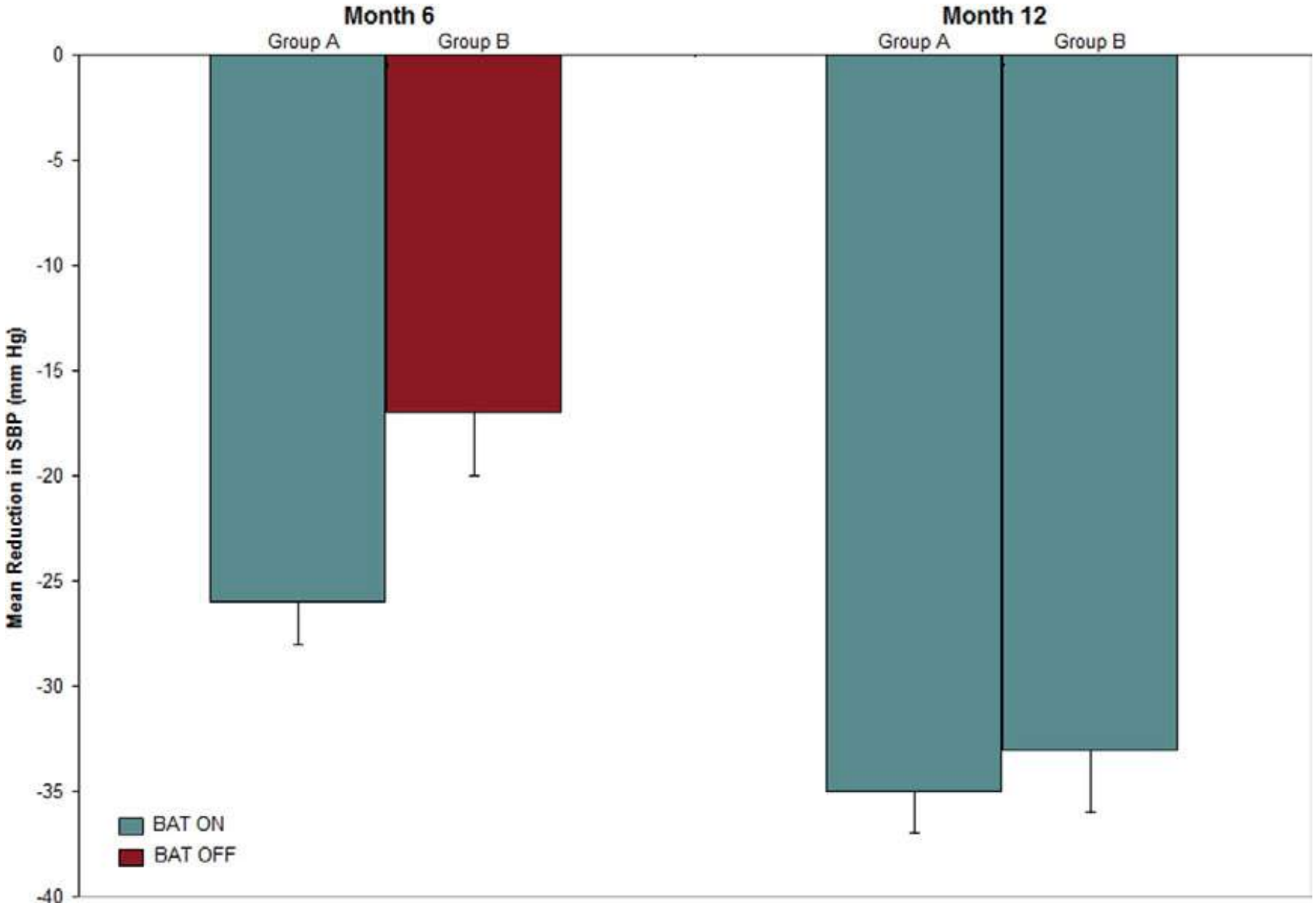
Baroreflex Activation Therapy Lowers Blood Pressure in Patients With Resistant Hypertension

Results From the Double-Blind, Randomized, Placebo-Controlled Rheos Pivotal Trial

256 Patients



Bisognano et al., J Am Coll Cardiol. 2011;58(7):765–73



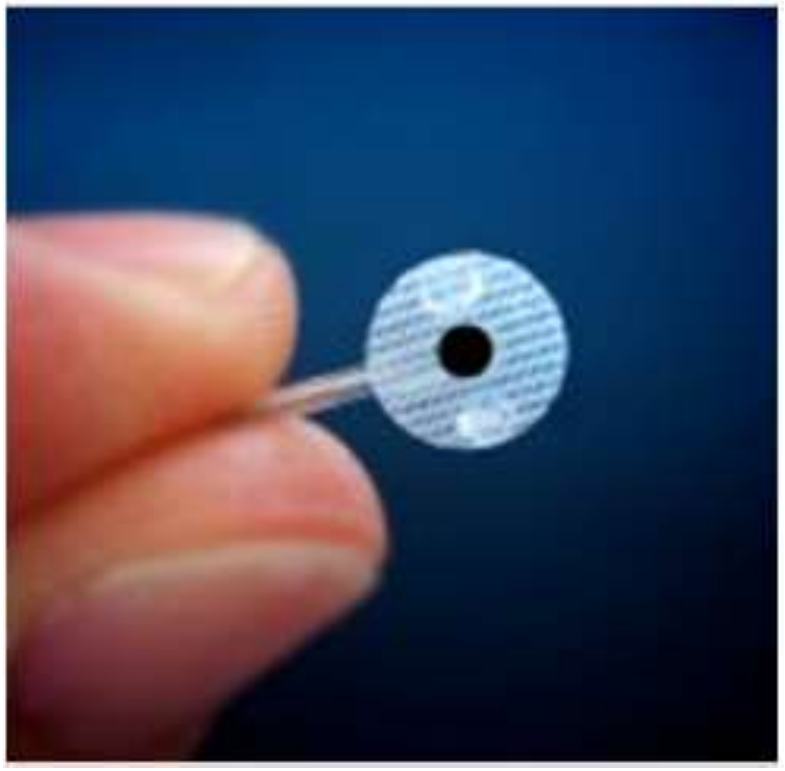
Bisognano et al., J Am Coll Cardiol. 2011;58(7):765–73

Summary of Adverse Events

Procedural	68 (25.5)
Surgical complication	13 (4.8)
Nerve injury with residual deficit	13 (4.8)
Transient nerve injury	12 (4.4)
Respiratory complication	7 (2.6)
Wound complication	7 (2.6)
BAT	
Hypertensive crisis (Group A)	9 (5.0)
Hypertensive crisis (Group B)	7 (8.3)
Device	34 (12.8)
Hypertension-related stroke	6 (2.3)

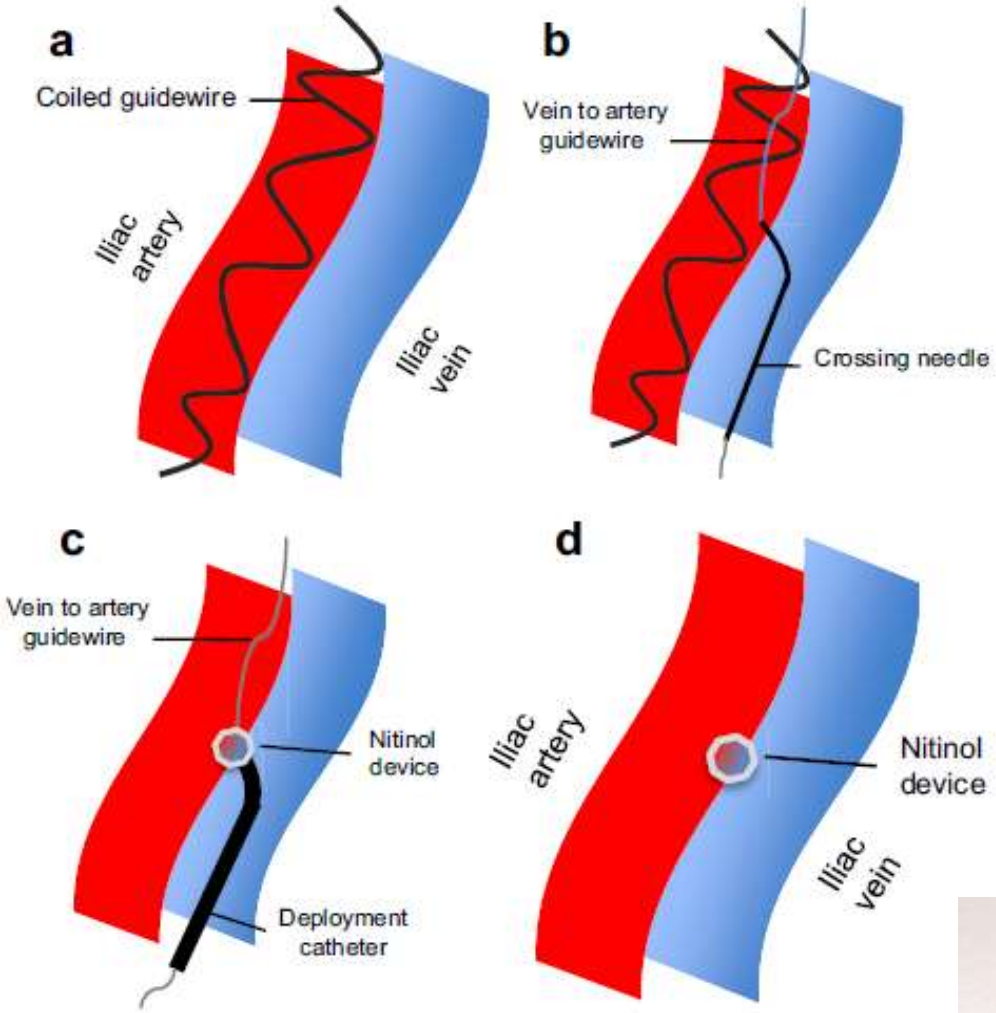
Bisognano et al., J Am Coll Cardiol. 2011;58(7):765–73

Barostim neo™ system



3. Arteriovenous Fistula

- AVF between iliac artery and vein.
- Originally developed to treat patients with COPD by ↑ COP and O2 delivery
- Retrospective analysis; significant fall in BP due to:
  - ↓ VR, ↑ COP.
  - Enhanced tissue O2 delivery → ↓ sympathetic overactivity
  - ↓ cardiac load



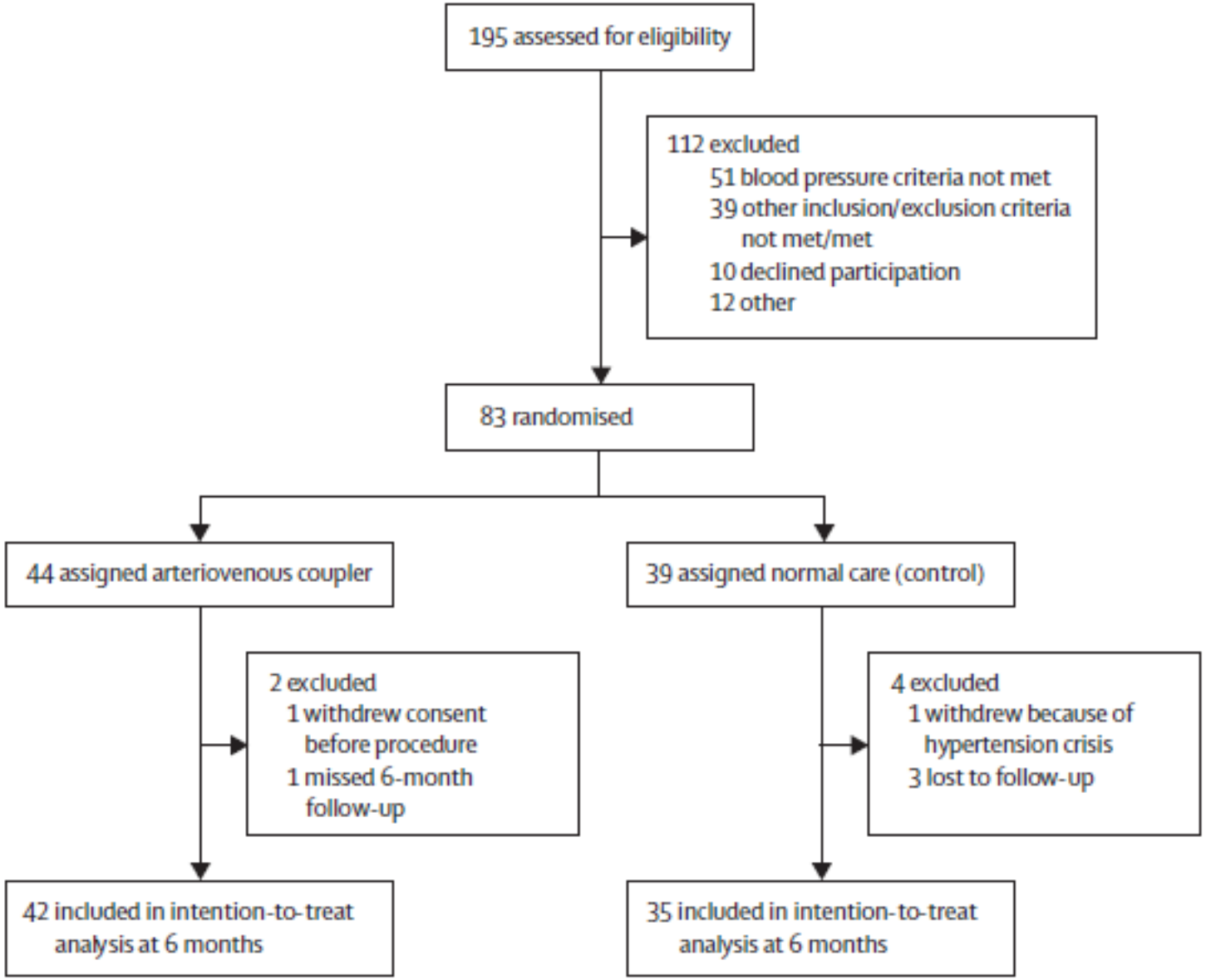
Faul et al., J Vasc Surg. 2014;59(4):1078–83.

Arteriovenous ROX Coupler

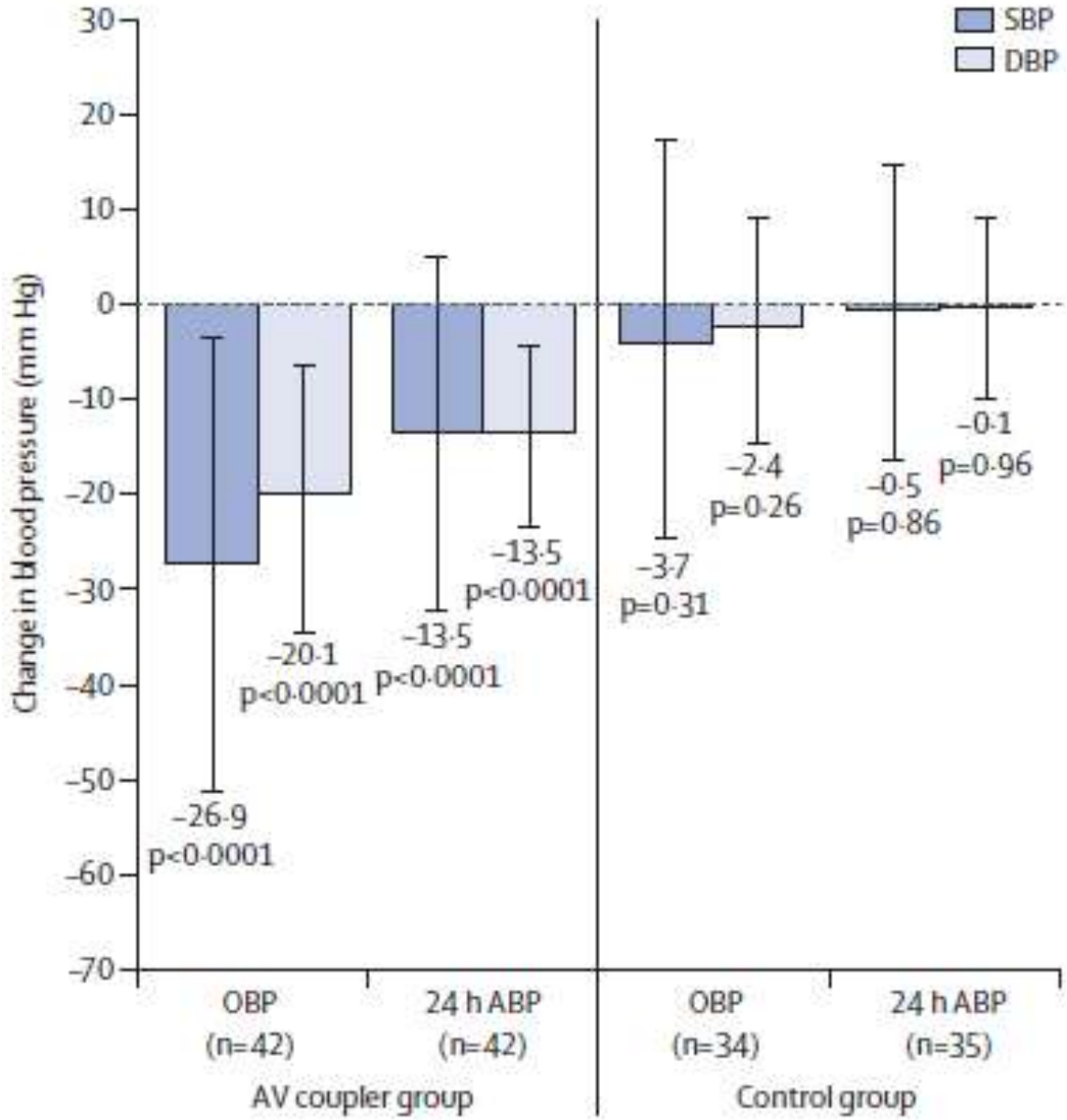
Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial

*Melvin D Lobo, Paul A Sobotka, Alice Stanton, John R Cockcroft, Neil Sulke, Eamon Dolan, Markus van der Giet, Joachim Hoyer, Stephen S Furniss, John P Foran, Adam Witkowski, Andrzej Januszewicz, Danny Schoors, Konstantinos Tsioufis, Benno J Rensing, Benjamin Scott, G André Ng, Christian Ott, Roland E Schmieder, for the ROX CONTROL HTN Investigators**

www.thelancet.com **Published online January 23, 2015 http://dx.doi.org/10.1016/S0140-6736(14)62053-5**

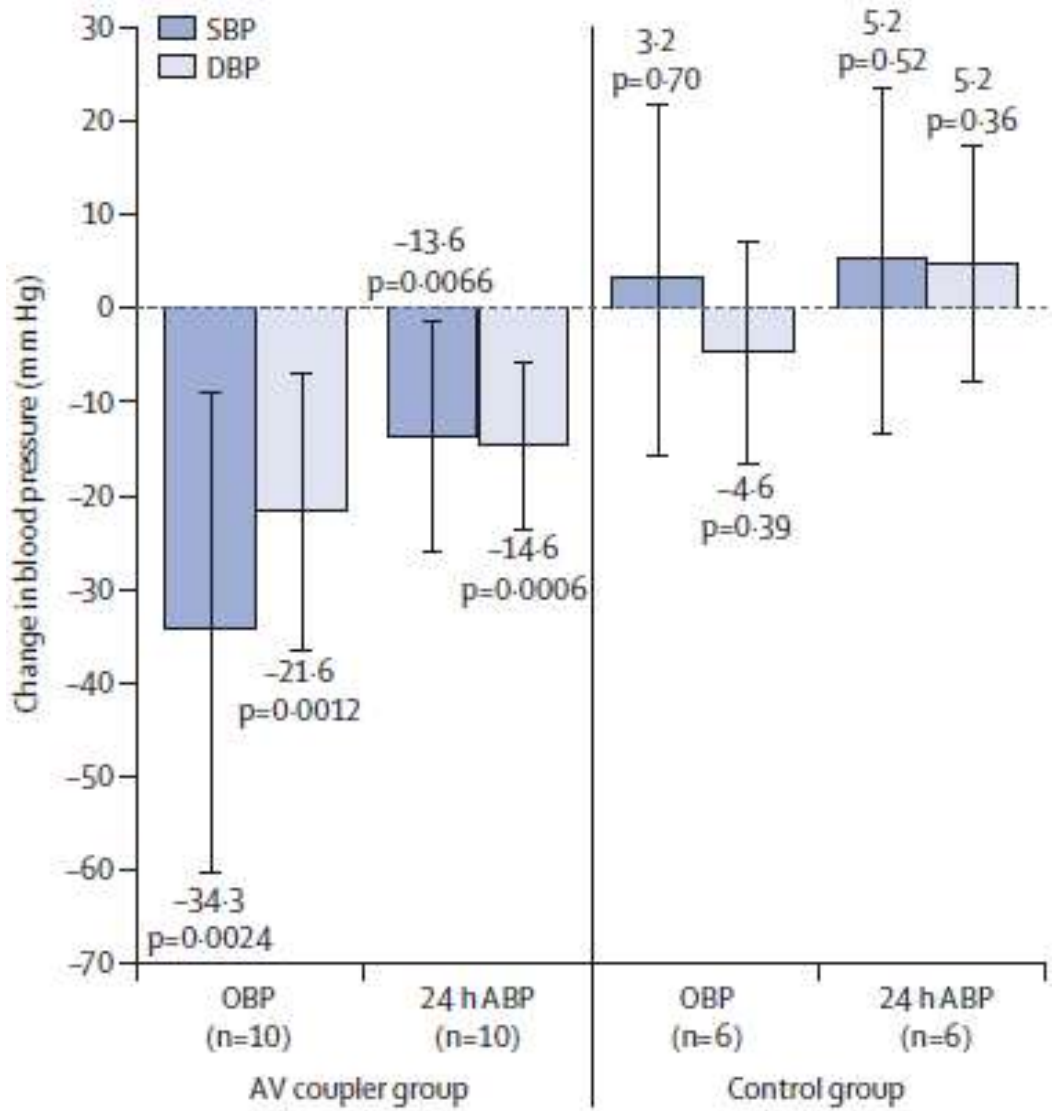


Lobo et al., lancet. Published online January 23, 2015



Lobo et al., lancet. Published online January 23, 2015

16 patients with previous RDN



Lobo et al., lancet. Published online January 23, 2015

Conclusion

- Resistant hypertension remains a challenging clinical problem that will increasingly become more common.

- Causes of resistance should be considered when blood pressure does not respond satisfactorily to a rational triple antihypertensive regimen that includes a diuretic.

- Careful assessment of the volume status and using aldosterone antagonists as the 4th antihypertensive agent is a cost effective strategy

- Newer interventional therapies may become a viable option in the future for unresponsive or intolerable patients to conventional therapies, but after good RCTs.

THANK YOU